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ADDRESS BY THE VICE-PRESIDENT

Metallic Sutures and Early American Gynecology*

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IT IS well known that Dr. Phillip Syng Physick, the father of American surgery, was not satisfied with the sutures then in use, and that his nephew, John Syng Dorsey, carried on some experiments with absorbable sutures. Whether or not he turned his attention to metallic sutures, I have been unable to learn. At any rate, two of Physick's pupils did some remarkable work with metallic ligatures and sutures. In 1829 Dr. H. S. Levert¹ published his "Experiments on the Use of Metallic Ligatures" in the *American Journal of the Medical Sciences*. Levert ligated the carotid and femoral arteries in dogs with various metallic ligatures and with silk. Around the silk ligatures, collections of pus were invariably found, but the metallic ligatures became "encysted" without producing inflammation. He said that Physick suggested the use of lead, since lead bullets remained in the tissues without causing inflammation, but, so far as Levert knew, no one had actually tried ligatures of this material. About the time that Levert was carrying on his experiments, Dr. J. P. Mettauer, another of Physick's pupils, was actually using lead sutures. The work of Levert was referred to by Bozeman³ and Sims,² but seems to have escaped any further notice.

In the anniversary oration of the New York Academy of Medicine in 1858, entitled "Silver Sutures in Surgery," Marion Sims² makes the statement that the silver suture was the greatest surgical discovery of the nineteenth century. He attributes to it his success, and also the founding of the Woman's Hospital of the State of New York. Sims is frequently spoken of as the father of modern

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gynecology. Therefore metallic sutures are the very foundation of the American Gynecological Society. Sims leaves one under the impression that silver sutures are his own invention. The editor⁴ of the *New England Journal of Medicine* says "we can perhaps, after all these years, forgive Sims for his bombastic language, for he richly deserves the credit of perfecting this operation (for vesicovaginal fistula) and of making it clear to the medical profession that the procedure was only consistently successful with the use of the Sims's position, the Sims's speculum, the special needles, and the inlying catheter that he had devised, and, finally, the silver sutures."

I am in complete agreement with this editor, except that there is more to the history of metallic sutures in general and silver sutures in particular than is indicated by either the editor or by Sims. According to Sir James Y. Simpson,⁵ Hippocrates and the ancients used gold and silver wire to hold teeth together in cases of fracture of the jaw. Celsus mentions gold and iron threads only to condemn them for use in animal tissues. The first time that metal was deliberately put into the tissues was in connection with attempts to cure inguinal hernia. Bernard Memis, Franco, Fallopius, and Paré applied what they termed the "golden stitch" or "golden tie" to the neck of the hernia sac. Aveling⁶ attributes the first use of metallic sutures to *Fabricius ab Aquapendente*. "After describing the ligature of Fallopius which was of thread, and like the ones which we, until lately, have been using, and that of Guido, which was made of metal, and hooked the two lips of the wound together, he says he provided himself with many flexible needles of iron or brass, made soft except at the point, over burning coals. These he passes through the lips of the wound and then turns back the extremities, the right to the left and the left to the right, fitting them over the wound, either straightly and plainly, or by making a knot." Fabricius gives the following reasons for preferring such sutures: (1) Iron does not eat into the flesh. (2) It does not ulcerate out. (3) It does not stretch and break. (4) It is not rotted by the discharge. Aveling was so impressed by the sutures of Fabricius that he had some made for himself, but so far as I know did not report upon their use.

In the eighteenth century Purmann⁵ of Breslau used silver to advantage in wounds of the tongue, and in 1746 Mihles⁵ speaks of using silver and gold threads in the repair of harelip, but Dieffenbach⁵ is credited with being the first modern surgeon to use metallic sutures. In a paper on staphylorrhaphy, published in 1826, he⁷ reported several cases in which he used lead thread to close the defect in the palate. He spoke of the advantage of twisting the wire, over having to tie a knot deep in the oral cavity. It should be remembered that there was no anesthesia in those days. Dieffenbach, being professor of surgery in Berlin, was an important personage, and his article was abstracted in great detail the same year in the *Lancet*.⁸ However, metallic sutures did not become popular in Europe. Gosset⁹ of London used gilded silver wire in a successful vesicovaginal fistula operation in 1833, but there seem to have been no other reports. In fact, Simon¹⁰ of Heidelberg, after adopting Sims' technique in the fifties, went back to fine silk. He said, "I even not only consider it no

progress, but rather disadvantageous, on account of the difficult application and removal of the sutures, and I have not the least doubt that the time is not far distant when the metallic sutures for plastic operations, and especially for that of vesicovaginal fistula, will yield again to the more convenient sutures of fine silk."

It was in America, according to Sir James Y. Simpson,⁵ that the subject of metallic sutures received the greatest attention. In 1827, one year after the publication of Dieffenbach's article on staphylorrhaphy and its abstract in the *Lancet*, Dr. John P. Mettauer¹¹ of Virginia used lead thread in the successful repair of cleft palate. In his paper "On Staphylorrhaphy," published in 1837, he gives Dieffenbach credit for introducing lead sutures. In 1833 he¹² reported a case of ununited parturient laceration of the rectovaginal septum successfully treated with metallic ligatures, and in 1847¹³ seven cases of third degree lacerations of the perineum. Six cases were completely cured. The seventh case was partly relieved and refused a second operation. In 1840¹⁴ he reported the cure of a vesicovaginal fistula, and in 1847¹⁵ he reported a series of six cases. By 1855¹⁶ his series had grown to thirty cases, and he was convinced that every case could be cured. After Sims' report¹⁷ in 1852, the story is well known to everyone.

Dieffenbach, who is looked upon as the author of metallic sutures in Europe, did not recognize their importance, and failed in a field where their use in America attained such remarkable success. He said of vesicovaginal fistula (1836),¹⁸ "I have operated on a woman eighteen times and discharged her unrelieved, I have gathered large rooms full of these unhappy women from all parts of the country, and I have exhausted all resources and have cured but few." Mettauer recognized the value of metallic sutures, and used them not only in staphylorrhaphy but with equal success in perineorrhaphies and vesicovaginal fistula operations. Sims recognized their value and used them in all fields of surgery and convinced the world of their value.

I have been interested to find out the reaction of the general run of the medical profession to these changes in suture material. The files of the *American Journal of the Medical Sciences* serve well for this purpose, for it has been in continuous publication since before sutures were used. Its very first volume¹⁹ contains an abstract from Sir Ashley Cooper's Lectures on Surgery, "Considerable prejudice exists in this country, and we cannot help thinking, with some justice, against the use of sutures." Sir Ashley Cooper, however, says that it is quite a mistake to suppose that sutures are injurious, and that they should never be used, "for a wound often heals better with a suture and a cooling lotion, than with adhesive plaster." Levert's¹ article on metallic ligatures is noted in the references. In 1841 there was an abstract of an article by Thomas Nunneley²⁰ of Leeds recommending threads of caoutchouc for sutures. It is claimed that they can remain much longer without producing irritation of any kind and, being elastic, hold the divided parts in contact and adjust themselves to the swelling of the tissues. Interestingly, the threads were obtained from suspenders, where Marion Sims²¹ said he got his idea for silver

sutures. Other than Mettauer's articles in 1833, 1837, and 1847, there are no more notices of sutures until Sims'¹⁷ classic article in 1852. After that, references to sutures became more frequent. In 1858,³⁰ there is a note that Professor Simpson used platinum wire as being more easily tied than the silver recommended by Dr. Sims. In 1859 Hodge²² has a report of his experiences with annealed iron wire, lead wire and silver wire in various operations. He preferred lead as did Spencer Wells²³ writing in the *Medical Times and Gazette* several years before. In 1859 Emmet²⁴ reported on the use of silver ligatures and sutures in amputation of the breast. In 1863, W. N. Chipperfield²⁵ of Madras is quoted as speaking "favorably of metallic sutures introduced into use by our ingenious countryman, Dr. M. Sims." In India he used iron wire.

Thus we see that the bacteriologic aspect of wound healing was solved by metallic sutures, even before men knew that there were bacteria. When antiseptics and later asepsis began to be practiced, metallic sutures became relatively less important. With Listerism it was possible to use catgut, and Lister²⁸ himself was a great advocate of catgut. The physical properties of catgut were more conducive to easy manipulation. There was another factor in wound healing, the elucidation of which awaited the genius of Halsted.³¹ Halsted³² showed that mass ligatures and sutures caused tissue necrosis, often microscopic in size, but important nevertheless. By tying off individual blood vessels and by closing the wound layer by layer with carefully placed sutures, one got better healing. Fine silk fitted in better with Halsted's meticulous technique, and in the Halsted era metallic sutures practically disappeared.

With improved metallurgic methods, stainless steel wire can now be made as fine as the finest silk. In 1932²⁶ Babcock introduced alloy steel wire for ligatures and sutures. The whole subject has been reopened, and the effect of sutures on wound healing has been restudied with modern methods. It has been found that the tissue reaction as seen under the microscope varies with the kind of suture material²⁹ used. It is greatest with catgut, not so great with silk, much less with cotton, and practically none with metallic sutures. It is interesting to note that these modern investigators confirm the accuracy of the work of Levert and the earlier observations of Fabricius.

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THE HUMAN CONCEPTUS DURING THE FIRST TWO WEEKS OF GESTATION*†

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THE youngest human embryo was conceived, not naturally in the Fallopian tube of its mother, but in a watch glass in the laboratory. It was the last of a series of almost 800 eggs, all recovered from ovarian tissue, of which 138 were exposed by Mrs. Miriam F. Menkin and me to human spermatozoa in about 1 c.c. of Ringer-Locke's solution.^{1, 2} After a pencil drawing was made of this two-cell individual, it was regrettably lost. A few days later, however, another egg similarly treated began its personal existence by changing from a single cell that had been part of the maternal tissue into a two-cell autonomous structure (Fig. 1, A). Because none had been seen to do likewise without spermatozoa, and there were spermatozoa within the zona pellucida, it is probable that this two-cell organism is the result of conjunction of the male and female components. Some weeks later, similar procedures resulted in the production of two ova in the three-cell stage.

Studies of early cleavage stages in the monkey by Lewis and Hartman,³ and in the mouse by Wright and Lewis,⁴ together with ours in the human being, indicate that eggs are fertilized soon after ovulation, usually within twelve hours. The youngest naturally conceived human specimen is one recently found by Hertig.⁵ It consists of eight blastomeres (Fig. 1, B). From the condition of the endometrium and of the corpus luteum, we think it is about 72 hours old. The next oldest human specimen is probably abnormal. It is considered to be 4 days old, and yet consists of only nine cells, several of which have more than one nucleus.

From the meager human material comprising four eggs fertilized in vitro and three‡ segmented ova removed from uteri, we may at present deduce that during the first forty-eight hours following ovulation, the mature egg enters the tube, conjugates therein with the spermatozoon, and achieves segmentation into at least two blastomeres. During the next two days division has progressed to the eight-cell stage, and the egg on the third day may reach the uterine cavity. It does not increase perceptibly in size through the three-cell stage. At the eight-cell stage the unfixed morula is about one-half again as big as the unfertilized ovum.

*Read at the Seventieth Annual Meeting of the American Gynecological Society, the Seignior Club, Montebello, Quebec, June 17 to 19, 1947.

†This study has been aided by grants from the Wm. F. Milton Fund, Harvard University; The Committee for Research in Problems of Sex, National Research Council; and The Carnegie Corporation of New York.

‡One additional specimen not illustrated was found to contain about twelve cells and is probably normal.

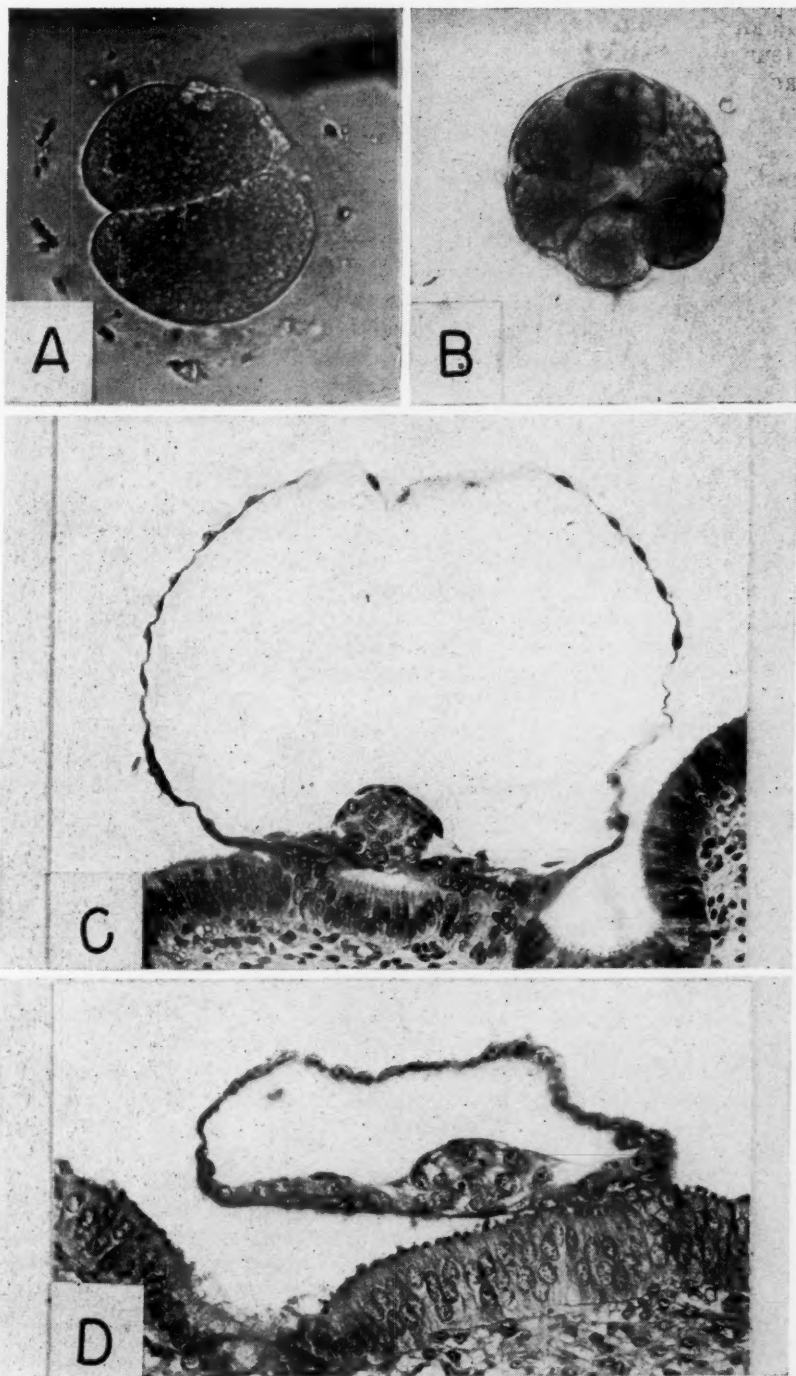


Fig. 1.—A. Two-cell human conceptus. Ovum fertilized in vitro. Two blastomeres, not quite of equal size, each containing single nucleus. One polar body. Several spermatozoa in the zona pellucida. ($\times 300$.)

B. Eight-cell human morula. Probably abnormal. Carnegie No. 8450. ($\times 300$.)

C. Blastocyst of rhesus monkey. In contact with endometrium. Carnegie No. 610. ($\times 200$.)

D. Nine-day blastocyst of rhesus monkey. Beginning its attachment to endometrium. (Figs. 1C and 1D are reproduced by courtesy and permission of Dr. Chester H. Heuser and Dr. George L. Streeter. In both figures the ventral surface of the inner cell mass is uppermost). Carnegie No. 520. ($\times 300$.)

Human development from the third to the seventh day is as yet obscure, but from Heuser's and Streeter's⁶ reports on several very early monkey ova we can imagine what must take place in the human being. Sometime between the third and sixth day, the multicellular morula acquires a central cavity to form the blastocyst (Fig. 1, *C*). Most of the hitherto contiguous cells spread out to form a cyst. Some of the cells remain grouped together at one pole of the blastocyst just within the enveloping layer. The newly formed spherical membrane will give rise to the trophoblastic or auxiliary structures: the smaller group of cells, to the embryo proper.

At nine days (Fig. 1, *D*) the multicellular monkey egg has differentiated into three major types of cells: those of the blastocyst wall which surrounds the fluid contained in the segmentation cavity; those much larger cells from which develops the embryonic disc; and the trophoblasts which are ready to eat their way into the endometrium. At nine days, the cystic monkey egg may still be free in the uterus, but about then, or soon after, it collapses and applies itself to the uterine wall. The human conceptus progresses more rapidly.

Thus, although already implanted, the youngest normally conceived human embryo we have seen is only about 7 days old (Fig. 2, *A*),* as judged by the time of coitus, the condition of the corpus luteum, and of the endometrium. Before fixation, it was not visible on the wall. After fixation, it was found to be about one-third of a millimeter in diameter. Stained sections showed that implantation was well advanced. We may say then that the human egg implants when about six days old and is comparable to the nine-day monkey blastocyst. How many of the first five days are spent in the tube, we do not know. As has been said, a specimen considered to be about three days old was found in the uterus. Perhaps the first day or two are spent in the tube where the morula is started. Probably during the fourth or fifth day the segmentation cavity is formed. Then occurs the differentiation into three kinds of cells, the primitive trophoblast of the blastocyst wall, the ectoderm of the embryo proper, and, beneath it, the endoderm. About the sixth day, the conceptus makes contact with the endometrium and the segmentation cavity collapses, as it does in the monkey. The newly differentiated syncytial trophoblast at the embryonic pole engrosses some of the superficial epithelium and as Streeter puts it, "forages" its way into this tissue.

After three days, as in our 9-day-old specimen (Fig. 2, *B*), the conceptus has become almost entirely surrounded by endometrium. It is now about one-half millimeter in diameter. The segmentation cavity has been redistended and within it is found the embryo proper. Two layers of this structure are well differentiated, and dipping into the ectoderm we see the enlarging amniotic cavity, which had been already visible two days earlier. This is bounded dorsally by the primitive amnion, the cells of which derive from the adjacent cytotrophoblast. The mass of syncytium has increased fully sixfold. Already spaces, lacunae, are formed within it. Separate at first, most, if not all, of these by the ninth day have communicated with each other to form a network of canals. Furthermore, the trophoblast has invaded the wall of at least one dilated sinusoid so that maternal blood, in small amounts, has flowed into the canals, thus bathing the syncytium. This is the origin of placental circulation.

Three days later, when the ovum is 12 days old (Fig. 2, *C*), progressive differentiation of the four tissues, already seen in their incipency, has built a sturdy, young organism. Over-all, it is about one millimeter in diameter, and is entirely within the endometrium, although the site of entry is not quite covered by closure of what will be the decidua capsularis. The embryo itself consists

*The stated ages of the embryo are made definite for "literary" reasons. Biologically these ages are only approximate.

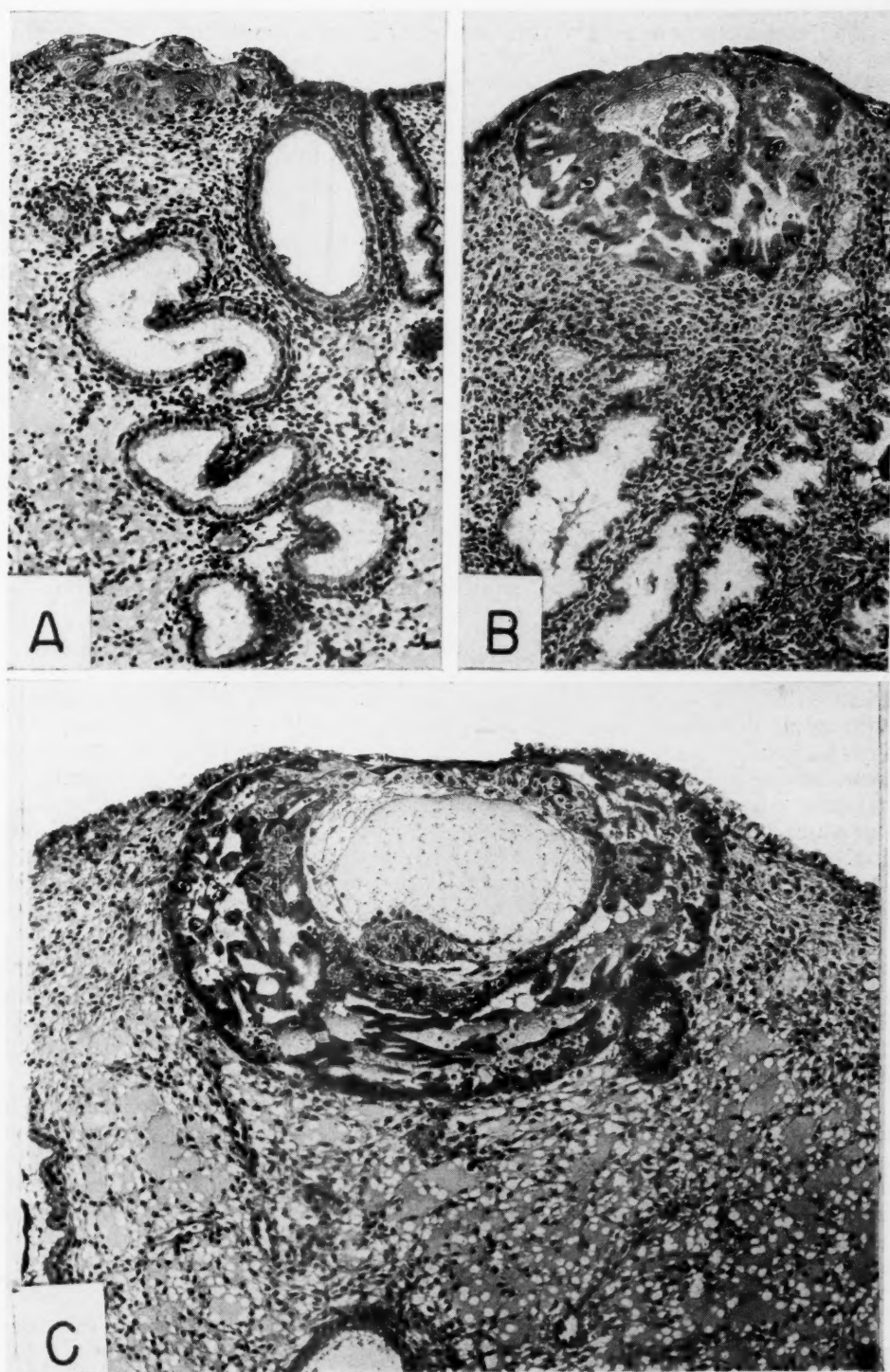


Fig. 2.—A. Seven-day human conceptus. Carnegie No. 8020. ($\times 100$.)
B. Nine-day human conceptus. Carnegie No. 8004. ($\times 100$.)
C. Twelve-day human conceptus. Carnegie No. 7950. ($\times 100$.)

of a pear-shaped plate about the size of a pinpoint, made up of a thicker pseudo-stratified ectoderm and a very thin ventrally situated endoderm. The cells of these two layers are delicately contiguous. They will later be separated by a third primary tissue of the embryo, the mesoderm. Dorsal to the ectoderm, bounded by it and the amnion, is the growing amniotic cavity that lies as a thin cyst on the back of the embryo. This still somewhat amorphous two-layer individual lies within a cavity fully five times its size. This is filled with fluid in which there is growing a diaphanous lacework of extraembryonic mesoblasts that divide this extraembryonic cavity, or coelom, into numerous chambers, one large and many small. The delicate net that joins the endoderm and with it surrounds the larger chamber is Heuser's membrane. We shall see that this is probably the *anlage* of the yolk sac. Surrounding this whole central space in which the embryo lies is the trophoblast, the all essential intermediary between the mother and the baby. This comprises two types of trophoblast derived from primitive tissue like that seen in the wall of the free monkey blastocyst: the cytotrophoblast that bounds the central cavity and the outer syncytium. The former gives rise to the mesoblastic network of the central cavity, and, on the outside, to the syncytium that is the commissary department of the whole organization. Since it made contact with the endometrium it has engrossed and digested the maternal stroma by which it grows, and dissolved a portion of a thin walled sinusoid, thus permitting increasing amounts of maternal blood to flow through the connecting lacunae formed within it. At this twelve-day stage, the syncytium constitutes about three-fourths and the cytotrophoblast the other one-fourth of the outer auxiliary portion of the conceptus.⁷

By the fourteenth day (Fig. 3, A), a significant change has occurred in the proportion and arrangement of the trophoblast that eventuates in a more efficient utilization of maternal blood. The inner cytotrophoblast grows rapidly. It started as not much more than a single-cell layer, but by the fourteenth day it is arranged in masses of single cells that project outward into the syncytium. Except in the outermost portion connecting with the endometrial stroma, this syncytium now forms only a thin layer of cytoplasm lining the lacunae. The proportions have changed: the greater part of the trophoblast is made of individual cells; there is proportionately less of the foraging syncytium.⁷ Once maternal blood is available it is apparently no longer necessary to consume much solid tissue.

Equally striking and significant are the papillary projections of the primitive mesoblast into the focal areas of the cytotrophoblast. This forms a thin wall over the projections, some of which are seen to extend into the lacunae. Within these evaginations, the primitive mesoblast builds a network in which will form the terminal placental blood vessels of the fetus. Thus do the villi arise.

Meanwhile, the mesothelial sac lying just ventral to the endoderm has become markedly smaller by a process not completely understood. It has become the yolk sac, an important structure for the further development of the embryonic end of the fetal vascular system. The amnion, too, is assuming its enveloping functions for we see its membrane has grown around the border of the ectodermal disc to make juncture with the mesothelial covering of the yolk sac. Most of the baby is now on its way into the amniotic cavity where we find it at term.

All this has occurred in about fourteen days. At the time of the first missed menstrual period, we have the ground plan of the placenta, a yolk sac, a completed amniotic cavity, and an embryo comprising undifferentiated ectoderm and a thin layer of endoderm. The whole conceptus is only about three millimeters in diameter, and is essentially engrossed within the endometrium. Sur-

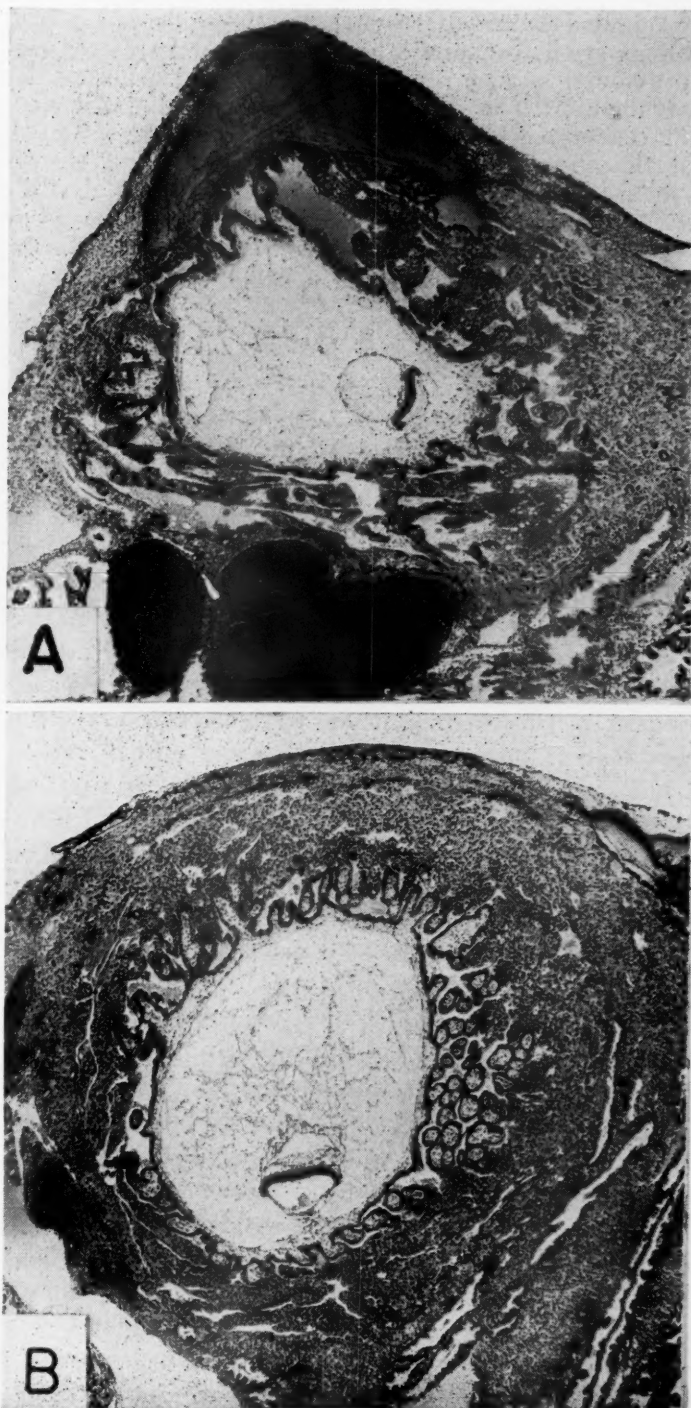


Fig. 3.—A. Fourteen-day human conceptus. Ventral surface of embryonic disc is to the left. Carnegie No. 7801. ($\times 35$.)

B. Sixteen-day human conceptus. Ventral surface of embryonic disc is uppermost. Carnegie No. 7802. ($\times 30$.)

rounding it are dilated maternal arteriovenous sinusoids that indirectly, by way of the intervillous space, communicate with the lumina of several glands into which blood has flowed in such a way that it can, and doubtless does, flow into and then out of the uterine cavity. Over one fourteen-day specimen (Fig. 3, *A*) is a mound of coagulated blood that has leaked through a tiny break in the trophoblast at the abembryonic pole. Toward the end of the sixteenth day (Fig. 3, *B*), we see what begin to look like mature placental villi surrounding the entire extraembryonic cavity. In serial sections, these are shown to be branches of the mesoblastic buds derived from the primitive extraembryonic mesoblast and surrounded by both kinds of trophoblastic tissue. At this time, the embryo, too, is entering the stage of previously known embryology. Heuser has reported the primitive streak as being in formation on the ventral surface of the ectoderm.⁷

As of June, 1947, our series of very young embryos, excluding those fertilized in vitro, amounts to twenty-six. Of the total, twelve are considered abnormal—47 per cent.

Three of them are in the stage of undifferentiating cleavage. Two of these are surely abnormal and the other is as yet considered so. Two of the implanted specimens consist only of trophoblastic tissue, having no embryo proper. Of the other imbedded ova, four have apparently normal embryonic discs but defective accessory structures; one has apparently adequate placenta-making material but a defective embryo; and in two, both parts of the conceptus are abnormal. Thus they all might and some surely would have aborted. Does this mean that 47 per cent of conceptions in normal fertile couples are doomed even before the first period has been missed? In some of these cases, the conceptus is so abnormal that probably no period would have been missed at all; the pregnancy would not even have been known to exist. These specimens are too few to give a conclusive indication of abortion frequency. They surely do not suggest that 47 per cent of recognized pregnancies may be aborted.

Our material has been collected by Hertig from uteri removed for various therapeutic reasons from women who had demonstrated normal fecundity, and who with one exception kept a record of the coital dates just preceding their operations. In each case there was a recent corpus luteum. To get these twenty-six specimens, one hundred twenty-two organs have been carefully searched. This might suggest a pregnancy rate of 21 per cent, but by correlating the dates of coitus with the ovulation period as determined by the endometrium, it was found that eighteen patients were probably not exposed during the ovulation phase. Among the cases in which coitus did occur during this time, 25 per cent were found pregnant. Unless some ova were missed, which is doubtful, we are led to believe that during any given cycle, a potentially fertile couple has not more than a 25 per cent chance of establishing a pregnancy that might persist long enough to suppress menstruation. It will be remembered that three of the specimens were found free in the uterine cavity and at least two are abnormal. Their prospect of normal implantation is unpredictable.

These twenty-six fertilized ova with associated maternal tissue give strong indication as to the time of ovulation in the menstrual cycle. The age of each conceptus as estimated by Streeter and Heuser, together with the immediately

preceding menstrual habit of the patient, the age of the endometrium,⁸ and of the corpus luteum,⁹ all tend to prove that in long or short cycles, ovulation occurs about the fourteenth day before the onset of menstruation.¹⁰

Summary and Conclusions

1. Human ova obtained from unruptured follicles can be fertilized in the laboratory and cultured to the three-cell stage. All such eggs, though normal in appearance, are not equally susceptible to fertilization.

2. In nature, human eggs are probably fertilizable for not more than twelve hours. Spermatozoa are apparently capable of fertilizing the egg for at least forty-eight hours after ejaculation. The human egg reaches the eight cell stage in three days after ovulation.

3. The fertilized human egg may have reached the uterus as early as the third day after ovulation. On about the sixth day, as a blastocyst, comprising three differentiated tissues, primitive trophoblast, ectoderm and endoderm, it makes contact with and begins ingestion of the maternal endometrium.

4. When nine days old, i.e., during the tenth day of development (on about the twenty-fourth day of a twenty-eight day cycle), the ovum has become interstitial in the endometrium, and has an average diameter of about one-half millimeter. The embryonic disc, comprising ectoderm and endoderm is well defined. The amnion is in formation. The larger part of the trophoblast consists of syncytium in which has appeared many communicating lacunae. Entrance has already been made by the syncytium into a maternal sinusoid, thus permitting maternal blood to flood the lacunar system.

5. When twelve days old, the conceptus is almost one millimeter in diameter, the embryo itself is about one-tenth as wide, and lies in a cavity about five times bigger than itself. This extraembryonic coelom is lined by a network of a fifth tissue, derived from the cytotrophoblast, the extraembryonic mesoblast, or mesoderm (not to be confused with the actual mesoderm of the embryo which appears later).

6. By the fourteenth day, the amniotic sac has covered the ectoderm. The mesoblast has formed many extensions from the cavity into the cytotrophoblastic mass, and has stretched the proportionately diminishing syncytiotrophoblast into a thin covering layer that then lines the lacunae. In these papillary outgrowths, the extraembryonic mesoderm extends to form a supporting structure. Maternal blood fills the lacunar spaces. Endodermal cells have proliferated to form the definitive yolk sac. The conceptus after fixation is from two to three millimeters in diameter.

7. By the sixteenth day, branched villi of mature appearance, but without a completed vascular structure, are formed. The primitive streak appears on the ventral surface of the ectoderm.

8. Forty-seven per cent of twenty-six embryos are abnormal in either trophoblastic or dermal tissue or in both. Two of the imbedded specimens lack the embryonic disc or inner cell mass.

9. In one hundred twenty-two uteri of proved fertile women, one hundred four of whom had ovulated and been exposed to pregnancy during the ovulation phase, only twenty-six conceptuses were found. Assuming none was missed, this gives a fertility index of only 25 per cent.

10. Ovulation in twenty-six well authenticated cases occurred about the fourteenth day before the expected onset of menstruation.

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Discussion

DR. CARL HUBER, Indianapolis, Ind.—It seems to me that nothing can be more remarkable than this presentation. When one realizes the tremendous advances that have been made in human embryology in the past few years, the greatest credit must be given to Dr. Rock, his co-workers in Boston and at the Carnegie Institute.

As our knowledge increases, it becomes apparent how greatly the information obtained from the monkey has added to our knowledge of human reproduction. But it also has shown how important accurate study of these early stages in the human being itself has become. The variation of implantation from the sixth day in the human to the ninth day in the monkey is an example of these differences. This may perhaps be explained on the basis of the superficial implantation in the monkey and the interstitial type of implantation in the human. As our knowledge of these early stages increases, the time interval during which conception may occur seems to become shorter and more definite. If ovulation takes place with little variation fourteen days before menstruation and the ovum survives for only twelve hours, it is not surprising that only 25 per cent of apparently correctly timed exposures result in fertilization of the egg.

It is interesting that in an earlier report concerning twelve early embryos, 42 per cent were abnormal, and that in the present larger series 47 per cent showed abnormality. At that time it was suggested that this rate of abnormality, 42 per cent, was much higher than anticipated, and now that the series increases, the frequency of early abnormal embryos becomes still greater. It would be interesting to learn if as many of the abnormal ova were implanted on the anterior wall of the uterus as reported in the previous communication some years ago.

It is also very interesting to note the lack of hemorrhage associated with implantation until approximately the time of the next expected menstrual period. It is clear from the pictures that there was practically no hemorrhage until from the twelfth to the fourteenth day, and then considerable hemorrhage surrounded the ovum and broke through into the endometrial areas. As previously suggested, then, the appearance of blood at the time of the expected menstrual period may be a sign of implantation and the source of confusion concerning the time of onset of the pregnancy.

DR. NICHOLSON J. EASTMAN, Baltimore, Md.—In keeping with what we have learned to expect from Dr. Rock, this is a valuable and welcome contribution, since it recapitulates and integrates, particularly from the viewpoint of embryologic timing, the series of monographs issued during the past ten years under the authorship of Rock and his associates. This group of papers has opened up new horizons in embryology; and to say that it constitutes one of the major contributions to embryology and obstetrics of our time would be merely to reaffirm a fact recognized wherever embryology is known. These alterations which Dr. Rock has described so graphically in the early fertilized ovum as they occur from day to day may be regarded as the workings of the genes. They are the long-continued progressive effects of gene action. They are primarily genetic in character.

Because of the magnitude of the task of unravelling all of these morphologic changes which have been described, Dr. Rock and his associates have focused their attention on these phenomena and have chosen to say very little about a certain factor which may drastically affect this series of specimens. I refer to the role of environment in the development of the early ova, a problem which is of far-reaching clinical importance. Environment may produce decided changes in the development of the early ovum. For instance, in primitive forms of life, it is well known that changes in the cell concentration of the fluid surrounding the developing ova may work havoc with normal development. The same is true in many experimental animals when their diet is deficient in certain food essentials.

One of the most interesting ways in which environment may produce changes of ovular development is to be found in tubal twinning. We know that when twins are encountered in the uterus the ratio of monozygotic twins to dichorial twins is one to three; but, as Arey showed some years ago, when twins are implanted in the tube, this ratio is no longer one to three, but fifteen to three. In other words, there is something about the environment which the ovum encounters when it implants in the tube which brings about abnormality at an early stage and results in twin embryos.

Another role environment plays in causing deviations from the normal in ovular development is in diabetes. It is common knowledge that congenital anomalies in infants of diabetic women are not infrequent. In a few months Dr. Priscilla White will report a large series of children of diabetic mothers, in which she will cite a high incidence of developmental anomalies. Some of these defects may be minor, it is true, but the figure which she will report is about 25 per cent.

The Australian experience with rubella is another example of how environment may affect embryologic development. Dr. Rock reports an incidence of 47 per cent of abnormal ova; and the question arises whether some of these may not have been due to the pathologic changes which prompted the hysterectomy. He pointed out that these hysterectomies were done advisedly, and I am wondering whether these alterations, through producing unfavorable environment, may not have played a role in his very high incidence of defective ova.

The importance of environment, then, in the development of the early ovum is well established; moreover, it has a very definite clinical bearing because the most common cause of abortion is a defective conceptus. But the question is: why is the conceptus defective? Is it the result of original faulty genes or the result of faulty environment? The embryologic work of Mall as well as Streeter shows that most abortions are due to faulty ova, and the latter, in their opinion, are usually due in turn to faulty genes. If this is true we are wasting our time in treating threatened and habitual abortion because this accident is foreordained. On the other hand, there is accumulating evidence to indicate that faulty genes are probably not as common as some have believed, and that faulty environment plays a larger role in abortion than was formerly thought. If poor environment does loom large in this picture, then we are fully justified in trying to correct it and in searching more intently than in the past to discover its causes. I hope Dr. Rock in his closing remarks will state whether he has been able to correlate to any degree whatsoever these abnormal ova with abnormal environmental conditions, and give us his general opinion in regard to the respective roles of the genes and environment in causing abortion.

DR. KARL M. WILSON, Rochester, N. Y.—I would like to ask Dr. Rock to describe the technique used in recovering the ova. More of this material could be obtained if more of us become interested in attempting to recover it and then arrange to send the material to Dr. Rock's laboratory or some other embryologic laboratory for study.

In discussing the development of the core of the chorionic villus, I wonder if he has observed anything in the way of delamination of the trophoblast as a source of origin for this tissue. Streeter feels that this is the important origin if not the only source of origin of the mesodermal tissue in the chorionic villi, that is to say a delamination of trophoblast and then its differentiation into mesoderm. In a seventeen-day specimen I described several years ago, it seemed to me that this could be demonstrated reasonably satisfactorily.

DR. THADDEUS MONTGOMERY, Philadelphia, Pa.—I understood Dr. Rock to say that the mesoderm is driven from the trophoblast into this tissue and that this cystotrophoblastic layer produces a synciotrophoblast. What is the relationship of this phenomena to the disappearance of the Langerhan's layer?

In the limited work I have done myself in this field, it has seemed to me that I have many times seen the pinching off of Langerhan's layer into the mesoderm core of the cells. The mesoderm often resembles the similar elements of Langerhan's layer. We know that the Langerhan's layer eventually disappears and it may be that it is due to the eventual disintegration of the layers. Certainly the microscopic appearance of tissues would suggest it does take place and it may be that the so-called protective cells of the placenta and the chorionic mesoderm are derived from the same order.

DR. EMIL NOVAK, Baltimore, Md.—When one stops to think that up to twenty-five years ago no one had ever seen a human egg except as it exists in immature form in the ovary or when, after fertilization, it has already implanted itself in the endometrium, the importance of these contributions of Rock and Hertig can be all the more fully appreciated. For many years the Miller ovum remained the real aristocrat among the young eggs which had been discovered, but in this egg, estimated to be about ten and one-half days old, the amnion had already been formed, and we could only speculate about its derivation, as well as about other early features, which have been largely clarified by the study of the much earlier stages which Rock and Hertig have made available.

One point which interested me greatly in these slides was the variation in the degree of decidual response in eggs which are presumably of about the same stage of development. The Miller egg, of which I was fortunate enough to see the original sections, showed almost no decidual change in the stroma cells, and yet one of the specimens we have seen today is of almost exactly the same age, and it shows a rather full blown transformation of the stromal cells into large, polyhedral and typically decidual cells. I wonder if Dr. Rock has been impressed with this variability in the degree of decidual reaction?

Dr. Eastman spoke of this work as representing a major contribution to embryology. Although I am not an embryologist, it seems to me to represent the most important contribution of our generation in this field.

DR. ROCK (Closing).—In answer to Dr. Novak's question about the endometrium: It is surprising how variable this can be in the different ages of eggs. Some of the endometrium is in the edematous phase, showing that the conceptus must have got into a tissue that had not gone that far, or else the edema had lasted longer than was to be otherwise expected.

Dr. Huber has called attention to the deciduallike reaction around the embryo. It seems to be a very localized effect.

Dr. Wilson will forgive me for not taking time to describe my method of selecting cases and Dr. Hertig's fairly simple but meticulous technique of examination, for the details have been published in *Contributions to Embryology*, number 184, page 131, Carnegie Institution of Washington Publication.

Regarding Dr. Montgomery's remarks: I expected the discovery that I am not an embryologist. I do not know where the mesoblasts come from. The extraembryonic meso-

blasts which have formed the network in the segmentation cavity come from the cytotrophoblast, and this network extends outward in the evaginations of the cytotrophoblast that will develop into villi.

The only pathology in the endometrium found in our cases was that associated with one of the abnormal eggs that had no embryo. This implantation site was polypoid. In the rest of them we could find no abnormality of the endometrium as far as the cytology of this tissue and its staining quality are concerned. There is much to be learned about maternal environment, for, as Dr. Eastman has brought out, this must have a great deal to do with growth of the ovum, especially in these early stages. It seemed at one time that eggs probably do not take much from their tubal environment. They needed warmth and moisture and transportation. Now we know the very young ova increase slightly in size, so they must acquire something. Of course, the zona disappears, but just how they carry on before they implant we do not know.

The question arose as to the site of implantation. Of the twenty-three implanted specimens, fourteen were normal. Of these, five were on the anterior wall, and nine on the posterior wall. Nine were abnormal. Of these, six were on the anterior, and three on the posterior wall.

Time forbids adequate discussion of the possible likely causes of abnormal development during the first ten days after fertilization. The determinants of cellular differentiation and orientation are obscure. I would suppose that the intrinsic protoplasmic quality of the ovum as affected by intrafollicular conditions and by age, as well as the modification of the directive genes of both egg and spermatozoön might affect the orderly cleavage and arrangement of blastomere quite as much as would environmental factors.

STUDIES OF THE HUMAN CORPUS LUTEUM*†

Corpus Luteum-Endometrial Relationships in Functional Uterine Bleeding*

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THE purpose of this paper is to present a histologic study of corpora lutea and endometriums in instances of functional uterine bleeding, and to discuss the relationships of these two tissues.

The term "functional uterine bleeding" is used here in the same manner as defined by Curtis.¹ He stated that this type of bleeding includes endocrinopathic cases with bleeding and also bleeding cases which may not be attributable to endocrine disorders. The material presented here may throw some light on the latter type of bleeding. Most authors include under the designation of "functional uterine bleeding" only those cases in which there is no associated gross pelvic pathology. It is our belief that "functional uterine bleeding" can occur and that the ovarian and endometrial tissue changes are identical, irrespective of the presence or absence of gross pelvic pathology. It is, therefore, not logical to exclude instances of such bleeding in the presence of gross pathology from the classification of "functional uterine bleeding" merely because of the presence of the pathology.

Material

The specimens in each instance were obtained by hysterectomy and oöphorectomy or by resection of the corpus luteum. The operations were performed during the bleeding phase, since it is during this period that most accurate interpretations can be made. Tissues obtained during a nonbleeding period cannot be accurately evaluated because one cannot foretell the date of onset of future bleeding, its duration, or its character, and because it is frequent for a normal cycle to be interposed amongst abnormal cycles.

SPECIMEN No. 335.—Aged 40 years; para iv, gravida iv; operated on day 27.

Menstrual history: Onset at 12 years; thirty-day cycles with three days flow until four months prior to operation. The last four cycles ranged from twenty-one to twenty-seven days in length with eight days flow.

Operation: Complete hysterectomy and bilateral salpingo-oöphorectomy.

Pathologic diagnosis: Multiple uterine fibroids and bilateral chronic salpingitis.

Corpus luteum: The corpus luteum was 1.1 by 1.0 by 0.6 cm. after fixation. The wall was in the usual folds. The granulosa lutein cells were not large, and histologically appeared to be intact functioning cells (Fig. 1). Only an occasional cell evidenced regression. The cells stained evenly and had large round

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or oval nuclei. Some nuclei were huge. Throughout the granulosa lutein layer there were many dilated blood-filled vascular channels. The connective tissue in the border about the central cavity was meager in amount, and was not arranged in an organized layer (Fig. 1). In some regions along the inner edge of the granulosa lutein layer small groups of partially degenerated nonluteinized granulosa cells extended into the cavity. This was observed frequently in young corpora lutea.



Fig. 1.—Specimen No. 335. The corpus luteum has persisted in the vascular stage with little evidence of regression until day 27 of the cycle and menstruation is beginning (see Figs. 2 and 3).

Endometrium: The endometrium was as thick as 0.2 cm. after fixation. There was a superficial infiltration of lymphocytes and leucocytes. The stroma was dense. The glands were squashed. The glands and gland cells were typical of a secretory pseudopregnant endometrium (Fig. 2). In one small region the surface epithelium was wanting, and the epithelial cells immediately adjacent were degenerated (Fig. 3). From this region there was evidence of bleeding into the uterine cavity with slight desquamation of tissue.

Interpretation: The corpus luteum had persisted in the vascular stage without evidence of degeneration for a prolonged time.

The glands of the endometrium were more fully stimulated than is usual with a corpus luteum in the vascular stage. Prolonged action of a functioning corpus luteum in the vascular stage might account for this excessive stimulation.

Involution, infiltration of leucocytes and lymphocytes, and localized bleeding indicated impending menstruation.

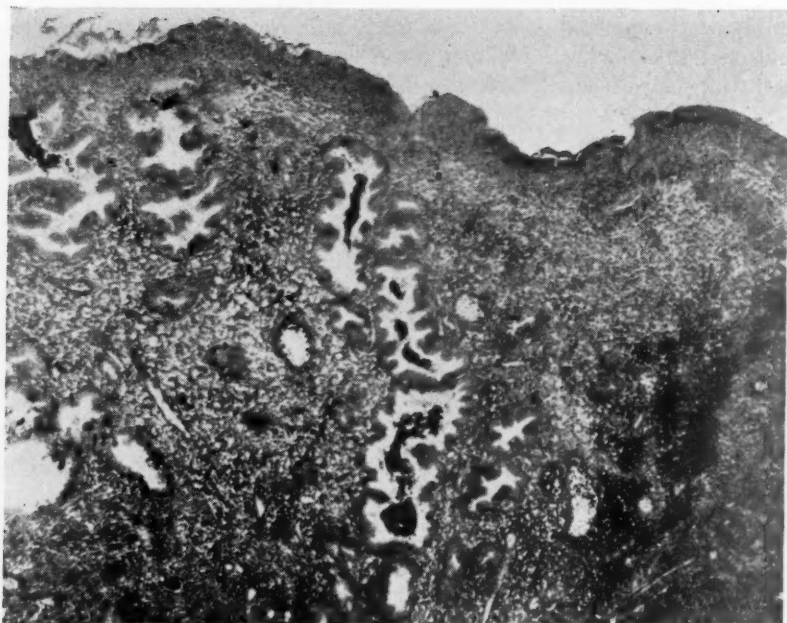


Fig. 2.—Specimen No. 335. The pseudopregnant type endometrium has involuted.

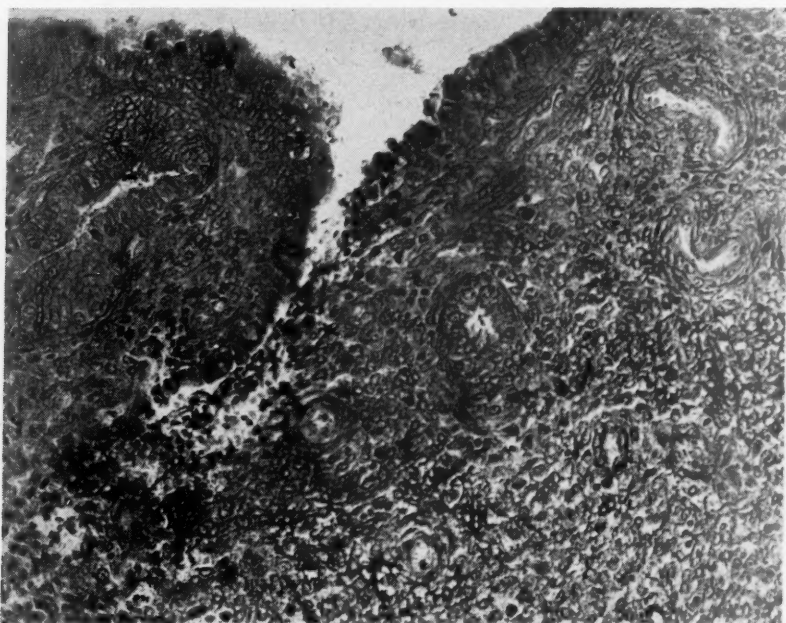


Fig. 3.—Specimen No. 335. In a small region desquamation of the surface epithelium of the endometrium has occurred and bleeding from this region is evident.

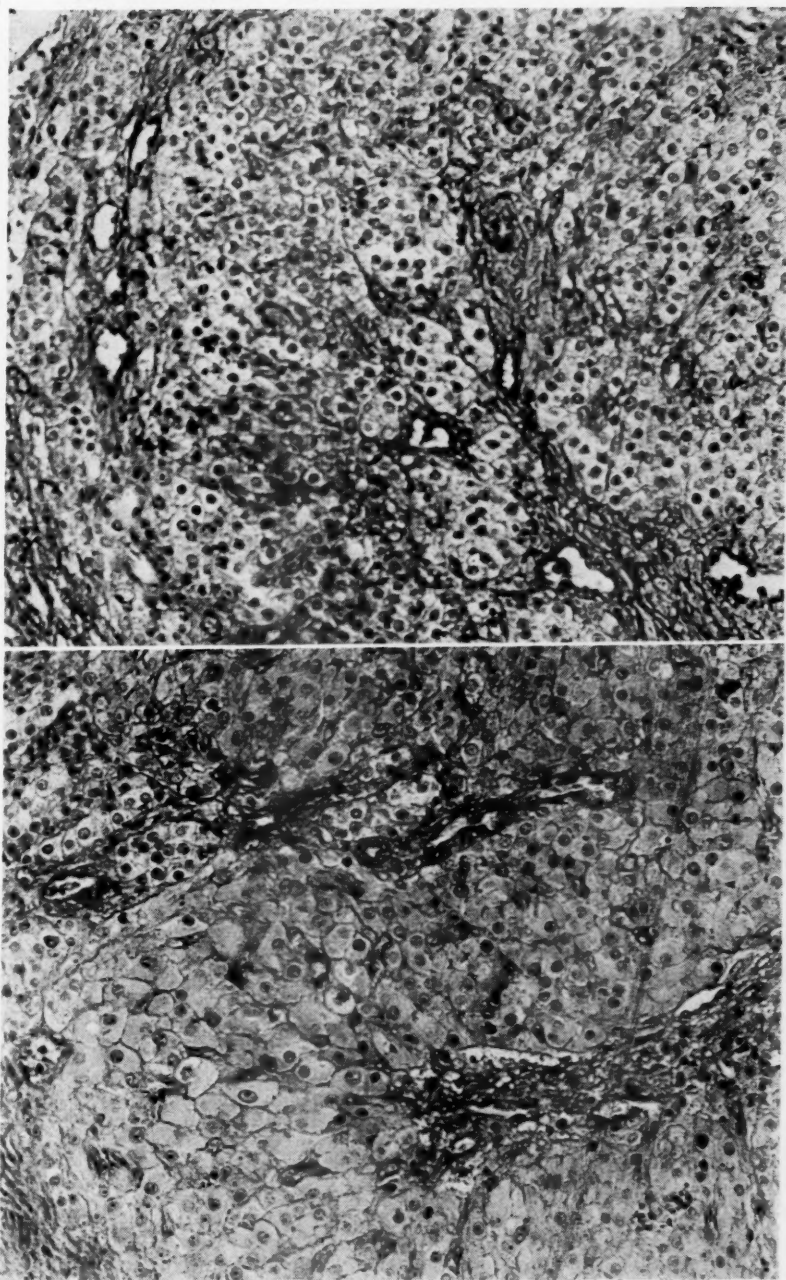


Fig. 4.—Specimen No. 332. Many of the granulosa lutein cells evidence degeneration. In other portions of the corpus luteum the cells evidence considerably less degeneration (see Fig. 5).

Fig. 5.—Specimen No. 332. On day 14 of continuous bleeding the granulosa lutein cells in this portion of the corpus luteum retain histologic evidence of functional activity. Some of the endometrial glands reflect this activity (Fig. 7).

The corpus luteum, however, had not undergone the degree of degeneration that is usually present at the onset of bleeding. In the life cycle of a normal corpus luteum some time is required to bring about complete regression of the gland after termination of the vascularization stage. In this specimen the vascular stage had persisted, and it was believed that complete regression would have required several more days. Since menstruation was impending, it was most probable that corpus luteum function would continue after the onset of bleeding, and that the period of flow would be prolonged as a direct result of prolonged activity of the corpus luteum.

This specimen represents an early phase of prolonged activity and life of the corpus luteum and irregular shedding of the endometrium.

SPECIMEN No. 332.—Aged 36 years; para 0, gravida 0; operated on day 14 of continuous bleeding.

Menstrual history: Onset at 14 years; twenty-eight to thirty day cycles, with four to five days flow until six months prior to operation. During these six months bleeding occurred every fourteen to twenty-one days. The last period of bleeding began fourteen days before operation, and bleeding was still present at the time of operation.

Operation: Hysterectomy and right salpingo-oöphorectomy.

Pathologic diagnosis: A single one centimeter intramural fibroid.

Corpus luteum: Prior to fixation the corpus luteum was 1.8 by 1.2 by 1.0 cm. It had a pale yellow wall and a gray-red centrum. Most of the granulosa lutein cells were shrunken, vacuolated, irregular, and had small nuclei (Fig. 4). In a few regions the granulosa lutein cells were large, had evenly stained finely granular cytoplasm, large round or oval vesicular nuclei, and appeared similar to functioning cells (Fig. 5). The central cavity had a dense well-organized connective tissue border. There was a moderate amount of connective tissue throughout the granulosa lutein layer. The theca cells were small, vacuolated, with small well-stained nuclei.

Endometrium: The endometrium prior to fixation was as thick as 0.2 cm. The surface was irregular and had no surface epithelial covering. At one place resting upon the surface was a mass of red blood cells with small intermingled degenerating endometrial gland and stromal tissues (Fig. 6). The endometrial desquamation in some regions reached down to and into the basal zone. Some of the glands had cells with peripheral secretory vacuoles (Fig. 7), and others showed evidence of antecedent secretory activity. Others were straight with narrow tall columnar cells and without evidence of secretory activity (Fig. 6). Only an occasional epithelial cell in mitosis was found, indicating that there was little active tissue growth. The stroma was dense and contained only a small amount of blood. No stromal cells in mitosis were found.

Interpretation: The degenerated granulosa lutein cells were no more degenerated than those seen at times in day 1 to 5 specimens.

Some groups of granulosa lutein cells showed little degeneration and appeared histologically similar to functioning granulosa lutein cells. Such cells in specimens fourteen days after onset of menstruation were not normally found.

The size of the corpus luteum was large for a day 14 specimen of the previous cycle.

The endometrium had not healed. There was no evidence of any active tissue growth.

Some glands retained secretory evidence and some did not.

This specimen represents an instance of prolonged activity of the corpus luteum and prolonged and irregular regression of the endometrium fourteen days after the onset of bleeding.

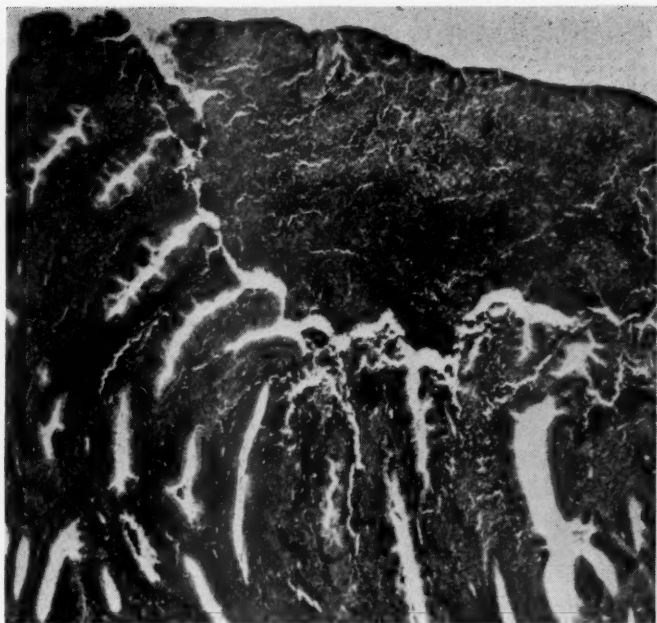


Fig. 6.—Specimen No. 332. The endometrium desquamation has occurred. Masses of cellular debris and blood cells rest upon the surface. Healing of the endometrium is lacking. Some of the glands are narrow, straight, and without secretory activity.



Fig. 7.—Specimen No. 332. The endometrial glands in some regions are secretory in character indicating continued and prolonged corpus luteum activity (see Fig. 5). Figs. 6 and 7 portray tissue changes typical of irregular shedding.

SPECIMEN No. 334.—Aged 40 years; para 0, gravida 0; operated on day 8 of bleeding.

Menstrual history: Onset at 13 years of age; twenty-eight day cycles, with eight days profuse flow for the ten years prior to operation. The last menstrual period began April 8, 1940, and the patient was still bleeding at operation on April 15, 1940.

Operation: Complete abdominal hysterectomy and bilateral salpingo-oophorectomy.

Pathologic diagnosis: A single 1 cm. intramural myoma, bilateral hydrosalpinx, and endometriosis.

Corpus luteum: The corpus luteum before fixation was 1.5 cm. in diameter with a wavy yellow wall. The central cavity contained a straw-colored fluid. Around the inner edge there was a layer of hemorrhage. Microscopically the wall of the corpus luteum was arranged in the usual folds. The granulosa lutein cells were for the most part large. Vacuolization of the cells was quite marked. Some cells had pyknotic nuclei, most, however, had intact round or oval vesicular nuclei. There was a marked vascularization of the entire layer. The connective tissue had grown through the granulosa lutein layer, but the amount projecting into the central cavity was meager and was not organized. There were frequent blood sinuses along the border of the central cavity. Along the inner edge in some regions were masses of small granulosa cells with vacuolated cytoplasm and pyknotic nuclei.

Endometrium: The endometrium was as thick as 0.2 cm. after fixation and staining. In most regions the surface epithelium was lacking. The glands project above the irregular endometrial surface. In most places the glands showed no evidence of secretory activity, were straight, and were lined by tall thin columnar cells with flattened nuclei. There were some glands that had centrally placed nuclei and had basal vacuoles. Epithelial cells in mitoses were extremely rare. The stroma was everywhere dense. Those portions of endometrium with intact surface epithelium were typical of a postmenstrual type.

Interpretation: On the eighth day of menstruation the corpus luteum was large, vascular, and had little evidence of regression.

Some portions of the endometrium had regressed, desquamated, and healed, while others were still in the process of desquamation. Those glands that had some secretory activity were of the early secretory type.

The findings were indicative of prolonged life of the corpus luteum with irregular and prolonged regression of the endometrium.

SPECIMEN No. 293.—Aged 44 years; para ii; gravida ii; operated on day 45 of bleeding.

Menstrual history: Onset at 12 years of age; twenty-seven to twenty-eight day cycles with four to five days flow. During the two and one-half years prior to operation the flow became profuse and prolonged, lasting as long as fifteen days. The last period of bleeding began Oct. 8, 1939, and had continued daily up to and including the day of operation, Nov. 21, 1939.

Operation: Hysterectomy and bilateral salpingo-oophorectomy.

Pathologic diagnosis: Uterine myomas and chronic fibrous salpingitis.

Corpus luteum: The corpus luteum before fixation measured 0.8 by 0.5 by 0.4 cm., and had a thick, wavy, yellow wall. The corpus luteum was histologically typical of a postvascular stage (Fig. 8). The majority of the cells were small, regular in outline, stained evenly, and had well-stained round or oval vesicular nuclei. Some cells in various regions of the layer were highly vacuolated, shrunken, irregular, and had pyknotic nuclei. The blood vessels throughout the layer were straight, thick walled, narrow, and, except in rare instances,

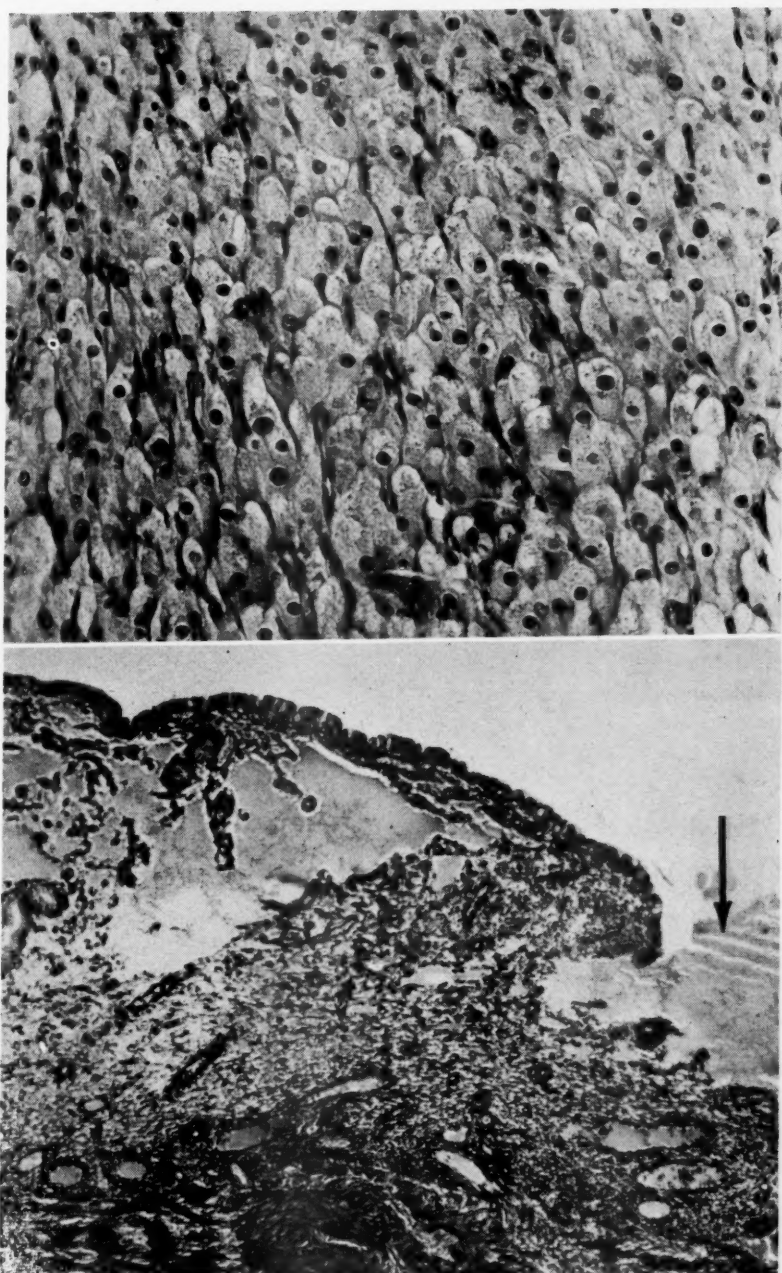


Fig. 8.—Specimen No. 293. On day 45 of continuous uterine bleeding the persistent corpus luteum is typical of the postvascular stage. Its secretory activity is indicated by the endometrial reaction (see Fig. 9).

Fig. 9.—Specimen No. 293. In this portion of the endometrium the glands evidence secretory activity. The intercellular fluid forms lakes. Adjacent (arrow) endometrium is partly sloughed and is bleeding (compare with Fig. 10).

contained no blood. The ingrowth of connective tissue was moderate, and that which extended into the central cavity was organized into a moderately thick border.

Endometrium: The endometrium after fixation and staining was as thick as 0.2 cm. The histologic appearance varied greatly in different portions of the uterus. In some regions the tortuous glands evidenced secretory activity (Fig. 9). These regions had intact surface epithelium. The large amount of intercellular fluid in the endometrium formed lakes in some places. The stromal cells were widely dispersed by this fluid. While this portion of the endometrium was secretory in character, it did not have the exact characteristics of a normal secretory endometrium. Adjacent to the above described region was a depressed region denuded of surface epithelium. The surface epithelial cells at the edges were degenerated. The stroma was densely packed as a result of involution with loss of intercellular fluid. Numerous large sinuses were present. Projecting into the cavity of the uterus from this region were masses of erythrocytes, intercellular fluid, and some tissue fragments.

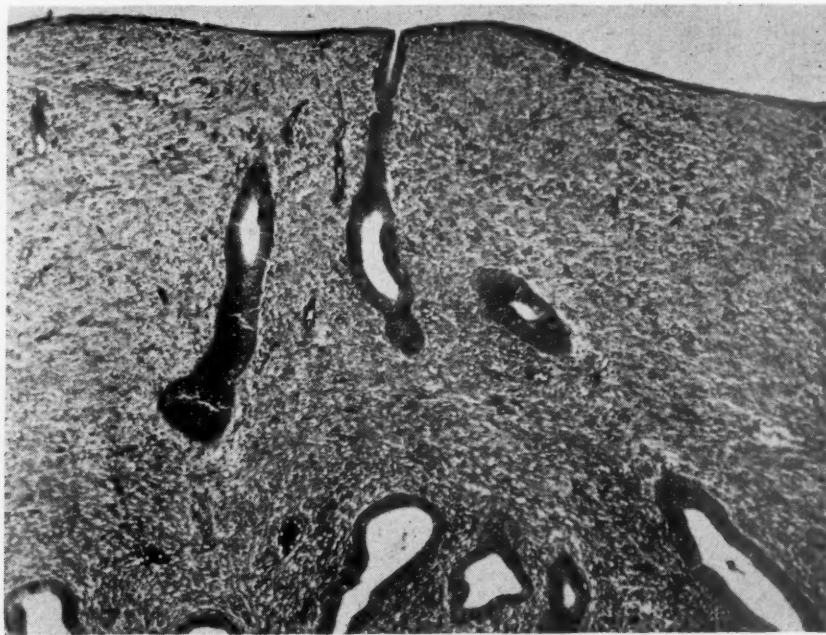


Fig. 10.—Specimen No. 293. This portion of the endometrium is typical of an immediate postmenstrual type. Irregular shedding characteristics are shown in Figs. 9 and 10. Prolonged activity of the corpus luteum (Fig. 8) is the direct cause of such endometrial tissue reactions.

In other regions the endometrium was typically post menstrual in type (Fig. 10). The intact surface epithelium in some places was columnar, in others cuboidal, and in still others was flattened. The glands were straight and had tall columnar epithelium without evidence of secretory activity. Mitoses, while present, were not numerous. The stroma was loosely arranged, and the spindle-shaped cells were small.

Interpretation: The corpus luteum had remained in the postvascular stage for a prolonged period of time, and, though small, maintained functional activity as indicated by the secretory character of the endometrium.

Some regions of the endometrium were still intact and secretory in character, while other regions had sloughed and had been completely repaired, although other portions continued to bleed.

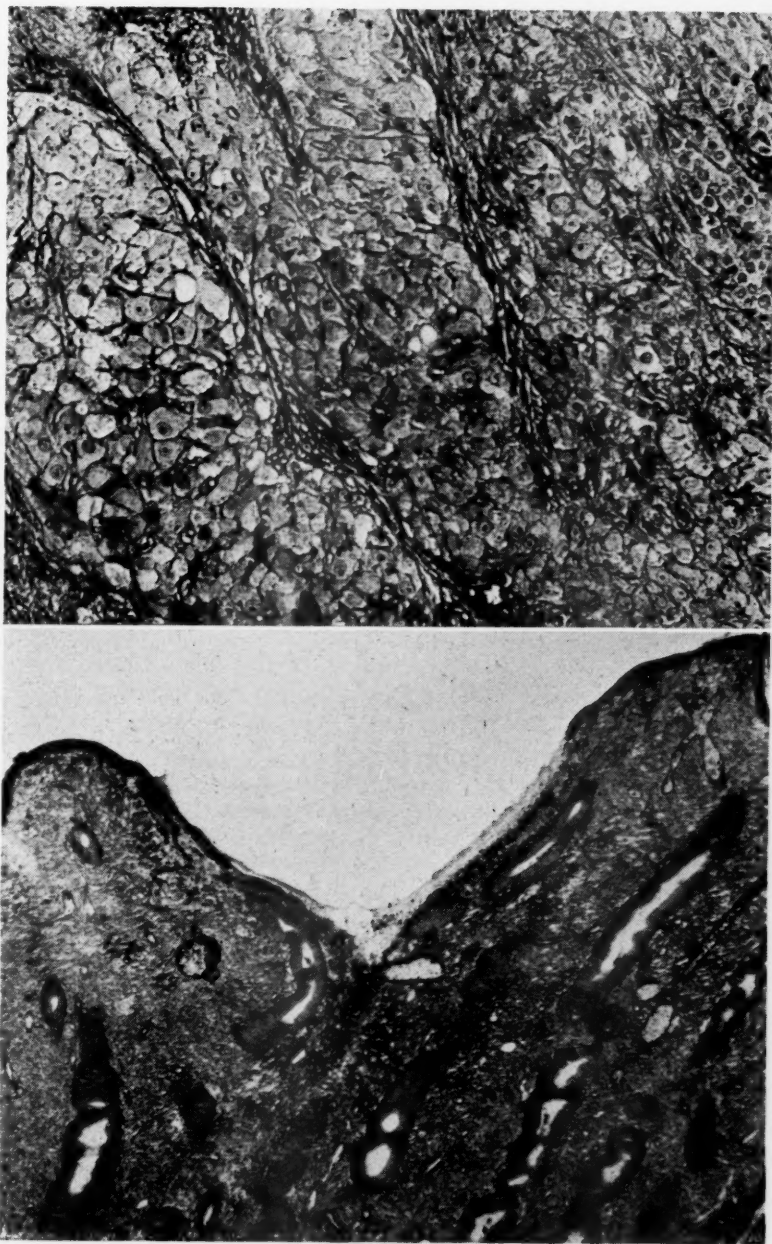


Fig. 11.—Specimen No. 265. On day 11 of continuous uterine bleeding most of the granulosa cells have degenerated but a few still retain mature characteristics. The life cycle of this corpus luteum has been prolonged.

Fig. 12.—Specimen No. 265. Some regions of the endometrium yet unhealed appear to be undergoing repair. The general picture is that of the final stage of prolonged bleeding just before the completion of healing. The histology of the corpus luteum (Fig. 11) is consistent with

This specimen demonstrates the wide range of endometrial variation that may occur with irregular shedding in instances of functional uterine bleeding associated with prolonged life and function of a corpus luteum. The inability of recently regenerated endometrium to respond to corpus luteum stimulation was also shown.

SPECIMEN No. 265.—Aged 38 years; gravida 0; unmarried; operated on day 11 of bleeding.

Menstrual history: Onset at 13 years of age; twenty-eight-day cycles with four to five days flow. During the ten years prior to operation the flow became longer and more profuse, and the cycles became shorter and irregular. A period of bleeding began June 6, 1939, and continued through July 20, 1939. On Aug. 13, 1939, bleeding began again and, when operated upon on August 23, 1939, bleeding was still present.

Operation: Hysterectomy and resection of corpus luteum.

Pathologic diagnosis: Uterus (no gross pathologic lesions of uterus, tubes, or ovaries were demonstrated).

Corpus luteum: The corpus luteum prior to fixation was 0.4 by 0.4 by 0.3 cm., had a wavy yellow wall, and a hemorrhagic centrum. The granulosa lutein cells in most regions evidenced marked degeneration. In many places these cells had been replaced by connective tissue. In some small regions the granulosa lutein cells were intact, shrunken, had evenly stained cytoplasm, and round or oval well-stained nuclei (Fig. 11). Such cells were not usually found in corpora lutea during this phase of a normal cycle. There was a marked ingrowth of connective tissue, and the border about the central cavity was dense, thick, and well organized. The theca cells were intact and evidenced little degenerative changes.

Endometrium: The fixed and stained endometrium was as thick as 0.3 cm. The stroma was loosely arranged, had considerable edema, and the cells were spindle shaped. The glands were straight, and were lined by tall columnar nonsecretory epithelium. Abundant epithelial cells in mitoses were present. Mitoses in stroma cells were frequent. These findings indicated active growth. These above findings were uniformly present throughout the endometrium, except for a few small regions where the surface epithelium was lacking. One such region was depressed below the level of the adjacent surface epithelium (Fig. 12). Its surface was irregular, and was covered with a narrow layer of blood cells. This represented a yet unhealed and still bleeding region. In another region not covered with epithelium there was a small mass of erythrocytes projecting above the surface and extending down into the stroma where it was continuous with a blood-filled sinus. The blood had escaped from a break in the wall of the sinus.

Interpretation: The corpus luteum was almost completely regressed from both a histologic and functional standpoint.

The endometrium was repaired in most portions, while in some the healing was incomplete. It is interpreted that healing would shortly have been complete.

The bleeding originated in the regions of delayed and incomplete healing of the endometrium, and was not typical of the normal menstrual processes.

This represents the terminal phase, immediately prior to completion of endometrial repair, of the prolonged life of the corpus luteum and of irregular regression of the endometrium.

SPECIMEN No. 257.—Aged 31 years; para iii, gravida v; operated on day 1 of bleeding.

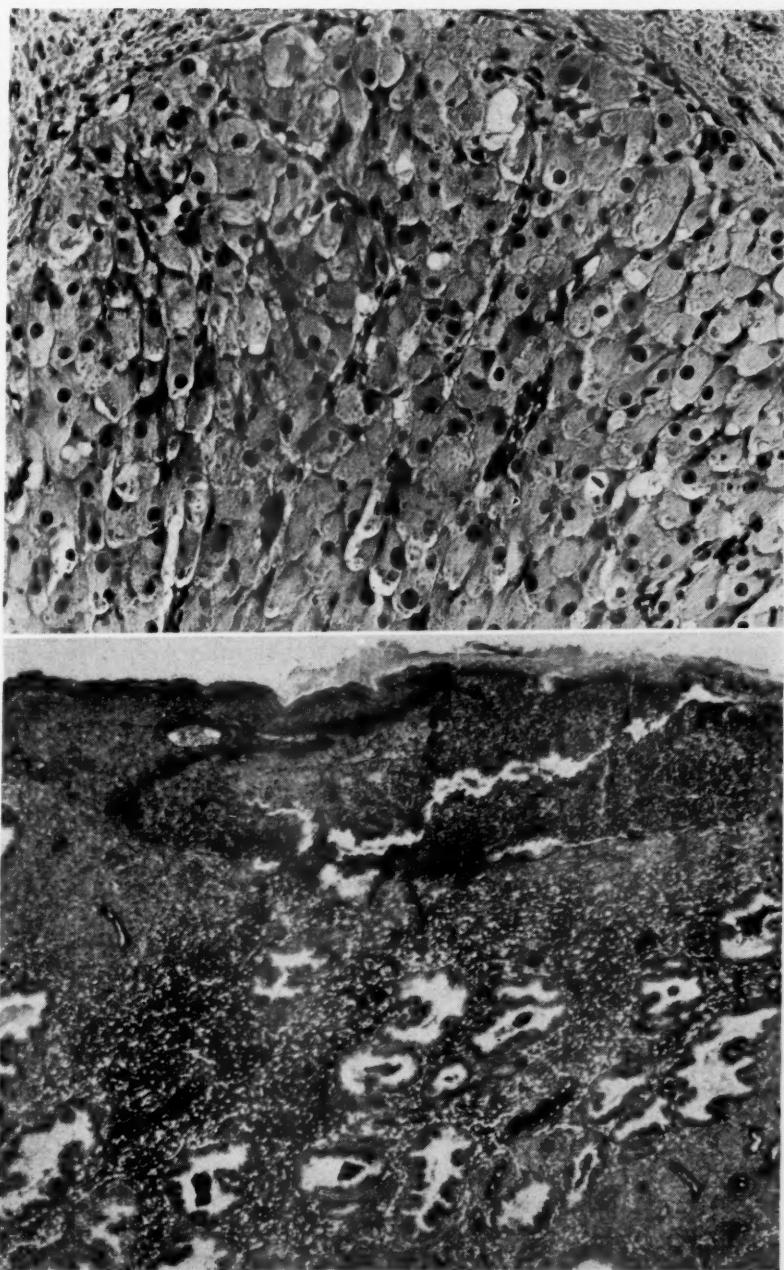


Fig. 13.—Specimen No. 257. This corpus luteum in the postvascular stage is functioning normally as indicated by the secretory character of the endometrium (Fig. 14). Ovulation in this patient must have occurred during a prolonged period of uterine bleeding.

Fig. 14.—Specimen No. 257. The endometrium has responded normally to corpus luteum stimulation. In a few regions the surface epithelium is disrupted, and bleeding is occurring from large venous sinuses immediately beneath the surface. The bleeding mechanism seems independent of the tissue changes of the endometrium, and also of the corpus luteum stimulation or withdrawal of stimulation.

Menstrual history: Onset at 12 years of age; twenty-eight-day cycles, with three to four days flow until six years prior to operation. During these six years the cycles were irregular, both too short and too long, and the bleeding phase lasted eight to ten days. On Oct. 12, 1938, a dilatation and curettage were done for diagnosis, and in an attempt to stop the bleeding. Bleeding ceased for three weeks after the dilatation and curettage, and then on Nov. 2, 1938, bleeding began again and continued until Dec. 15, 1938. On Dec. 22, 1938, bleeding began, and on that day a hysterectomy was performed.

Operation: Hysterectomy, left salpingo-oophorectomy.

Pathologic diagnosis: Uterus, tube, and ovary.

Corpus luteum: The corpus luteum prior to fixation was 2 by 1.5 by 1.5 cm. It had a wide yellow wall and a hemorrhagic centrum. Many of the granulosa lutein cells were shrunken, had irregular cell membranes, pyknotic nuclei, and vacuolated cytoplasm. Other cells retained their large size, had evenly stained cytoplasm, and round or oval nuclei (Fig. 13). The majority of cells, however, showed shrinkage in size. There was a moderate amount of connective tissue throughout the granulosa lutein and along the inner border. The blood vessels in most regions were empty and collapsed. Some occasional regions, however, had dilated blood-filled vascular spaces. In these regions cell degeneration was less evident.

Endometrium: The endometrium after fixation and staining was as thick as 0.45 cm. The glands were typical of the full secretory type (Fig. 14). They were large, serrated, had large cells with secretory vacuoles peripherally, and contained secretion in their lumens. The stromal cells were large, compactly arranged, and resemble predecidua. Spiral arteries reached to the surface epithelium. Involution had occurred.

There were some regions in which there was no surface epithelium. The epithelial cells at the edges of these gaps were degenerated. Filling the denuded regions and extending into the cavity of the uterus from large disrupted venous sinuses were masses of blood cells with some fibrin. These regions represented bleeding zones. The desquamation of endometrium was practically nil except for loss of surface epithelium. The large venous sinuses lay parallel to the surface.

Interpretation: The corpus luteum was histologically normal and was comparable to a postvascular, regressing stage (day 24 to 26). That its function was normal was indicated by the normal full-blown secretory character and the stromal response of the endometrium.

The endometrium in most regions had responded normally to estrogenic and progesterone stimulation.

The bleeding was not typical of normal menstruation since there was only disruption and bleeding from vascular sinuses without tissue loss to any extent.

Ovulation must have occurred during a period of bleeding and corpus luteum development progressed normally during bleeding.

The bleeding mechanism seemed independent of ovarian function.

SPECIMEN No. 266.—Aged 31 years; para iii, gravida iii. Operated on day 16 of bleeding.

Menstrual history: Onset at 13 years of age; twenty-eight-day cycles, with three days flow until the patient was 30 years of age. During the last year prior to operation the bleeding periods were profuse and lasted ten to fourteen days. There was also some intermenstrual spotting of blood. Bleeding began sixteen days prior to operation and had continued.

Operation: Complete vaginal hysterectomy, resection of corpus luteum.

Pathologic diagnosis: Small uterine myomas (tubes and ovaries normal).

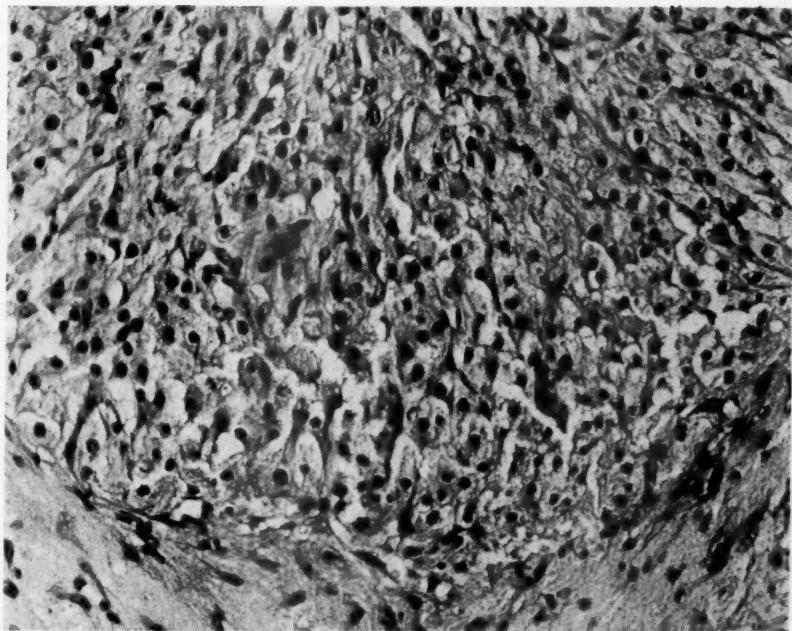


Fig. 15.—Specimen No. 266. The corpus luteum is young and is of the new cycle. The response of the endometrium (Fig. 16) to progesterone is consistent with the degree of development of the corpus luteum. Ovulation must have occurred during the sixteen-day period of uterine bleeding.

Fig. 16.—Specimen No. 266. The endometrium is early secretory in character. Independent of this normal tissue response certain small superficial regions of endometrium are bleeding. Desquamation is minimal. The bleeding seems independent of the corpus luteum and the general normal endometrial tissue response to stimulation.

Corpus luteum: The corpus luteum measured 2 by 1.5 by 1.2 cm. prior to fixation and had a wavy yellow wall. The granulosa lutein cells were not large, but in most regions were definitely luteinized. Many of the cells were vacuolated. There was extravascular blood scattered between the cells of this layer. In some places the cells were not yet luteinized, were elongated, and were arranged in streamerlike fashion. Along the inner margin the cells retained the granulosa cell characteristics, were not luteinized, were highly vacuolated, and had pyknotic nuclei. The ingrowth of connective tissue was scant in the granulosa lutein layer. A meager amount of connective tissue projected into the central cavity (Fig. 15).

Endometrium: The endometrium after fixation and staining was as thick as 0.4 cm. In all but a few small places the endometrium was covered with surface epithelium. The glands were similar throughout entire endometrium. They were slightly tortuous. The gland cells were columnar, had centrally located nuclei, and contained secretory vacuoles both in the basal and peripheral portion of the cells (Fig. 16). The loosely arranged stromal cells were spindle shaped and were widely separated by intercellular fluid. One of the regions void of surface epithelium was depressed below the general surface level, and was irregular. Projecting into the cavity of the uterus from this region were erythrocytes, edema fluid, and a small amount of stromal tissue elements.

Interpretation: The corpus luteum was young, was of the new cycle, and its development had progressed normally. Ovulation and corpus luteum development had occurred during a period of active bleeding.

The endometrium had responded normally for the most part to corpus luteum stimulation. The bleeding portion of the endometrium was neither in keeping with the remainder of the endometrium nor with the development of the corpus luteum.

The bleeding mechanism appeared to be independent of the corpus luteum function or failure of function.

SPECIMEN No. 273.—Aged 31 years; para iii, gravida v; operated on day 60 of bleeding.

Menstrual history: Onset at 15 years; twenty-eight-day cycles, with five days flow until two months prior to operation when she began to flow and flowed continuously to time of operation. At times this was only a spotting, and at times was profuse.

Operation: Hysterectomy and resection of corpus luteum from ovary.

Pathologic diagnosis: Multiple small uterine myomas.

Corpus luteum: The corpus luteum after fixation and staining was 1.1 cm. in diameter. There was a marked folding of the wall, considerable more than usually observed. The granulosa lutein cells were large, stained evenly, and had large round or oval nuclei (Fig. 17). Few cells evidenced regressive changes. There was moderate ingrowth of connective tissue. The connective tissue border of the central cavity was thin and loosely arranged. The blood vessels throughout the granulosa lutein layer contained few erythrocytes.

Endometrium: The endometrium after fixation and staining was as thick as 0.3 cm. The glands were somewhat tortuous. There was no secretion in their lumens. The gland cells were tall columnar with centrally placed oval nuclei. At the base of the cells there were large secretory vacuoles (Fig. 18). No cells in mitoses were found in a study of several sections from different blocks. The stromal cells were small and were widely separated by intercellular fluid. Spiral arteries did not reach to the surface.

One small portion of the endometrium had no surface epithelium. Extending into the uterine cavity through this denuded region was a large mass of

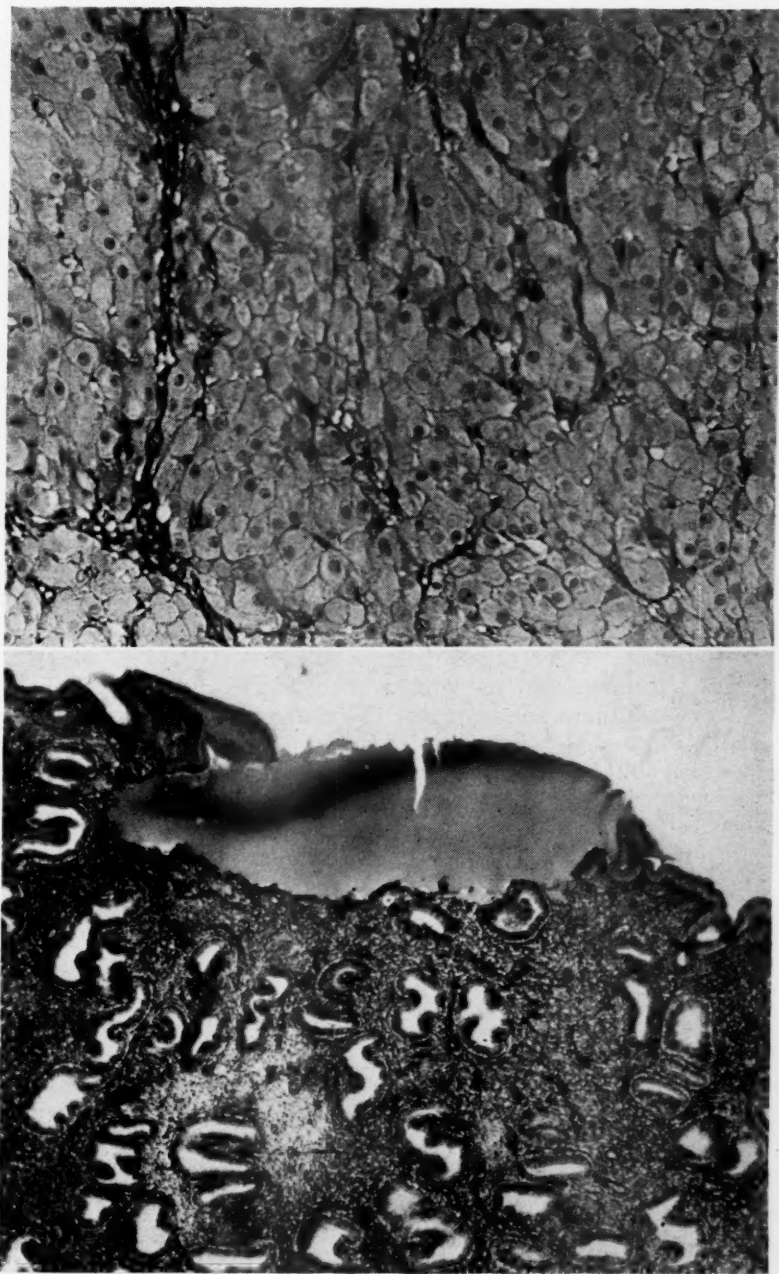


Fig. 17.—Specimen No. 273. This corpus luteum was removed from a patient who had been bleeding continuously for two months. It is functionally active. The relationship of the corpus luteum and the endometrium indicate that ovulation had occurred and corpus luteum development had continued during a period of prolonged uterine bleeding.

Fig. 18.—Specimen No. 273. The endometrium, except in a few small superficial regions, is typical of the early secretory stage. Bleeding is occurring from these regions. Desquamation of tissue is scant and is unlike normal menstruation. The bleeding mechanism seems independent of the general endometrial reaction and the corpus luteum.

intercellular stromal fluid. At the base there was some extravasated blood and a small amount of fibrin.

Interpretation: During the bleeding phase the endometrium had desquamated, bled, repaired itself, and had responded for the most part to the stimulation of the corpus luteum of the new cycle. One region was still not healed. The fact that the endometrium evidenced less change than anticipated by the appearance of the corpus luteum is explained on the basis that the endometrium was recently regenerated and consequently was not able to respond fully as yet.

Ovulation and corpus luteum development must have occurred and progressed normally during the period of bleeding.

It is indicated that the bleeding mechanism is independent of the corpus luteum function or failure of function.

SPECIMEN No. 375.—Aged 30 years; para 0, gravida i; operated on day 20 of cycle; day 1 of bleeding.

Menstrual history: Onset at age of 14 years; twenty-eight day cycles with five days flow until one year before operation. During that year the cycles were twenty-five days in length with a profuse flow for eight days. Last menstrual period was Feb. 1, 1941. Operated on February 20. Began to bleed February 19.

Operation: Hysterectomy and bilateral salpingo-oophorectomy.

Pathologic diagnosis: Multiple uterine fibroids and residues of pelvic infection.

Corpus luteum: The corpus luteum prior to fixation was 1.5 cm. in diameter. The granulosa lutein cells were luteinized, but were not yet large (Fig. 19). The granulosa cells nearest the source of blood supply were larger and more fully luteinized than those cells near the inner border. In the inner region of the corpus luteum the granulosa lutein cells were elongated as in young corpora lutea. In many regions these cells were separated by extravascular blood. This was particularly prominent near the inner border of the granulosa lutein cell layer. There was a moderate ingrowth of connective tissue, and the cells projected into the central cavity. The vascular structures in the layer are filled with blood. Chemical analyses of phospholipids and cholesterol esters (Weinhouse¹⁴) of one-half of the corpus luteum revealed values, expressed in per cent of moist weight of tissue, of 1.38 and 0.11, respectively.

Endometrium: The endometrium after fixation and staining was as thick as 0.53 cm. The glands were tortuous and had secretion in their lumens. The gland cells were large, had large oval nuclei located toward the bases of the cells, and contained secretory vacuoles in the peripheral portions. Many of the gland lumens contained blood. The closely arranged stromal cells were large and had oval nuclei. Most of the endometrium was of this character and was covered with epithelium. Involution had occurred and there was a superficial extravasation of leucocytes and lymphocytes (Fig. 20). Vaginal examination prior to operation revealed blood in the vagina and cervical canal. Gross examination of the endometrium at the time the uterus was surgically removed revealed one small bleeding region in the endometrium in the lower portion of the uterus. A block of tissue including this region was taken (Fig. 21). In the vicinity of this bleeding region the stroma was compact; there was a superficial infiltration of lymphocytes and leucocytes; and there was some localized extravasation of erythrocytes. The glands were straight and the gland cells showed no evidence of presently existing secretory activity. In the lumens of a few of the glands, however, there was some secretion indicating that some of the glands had had an antecedent secretory activity. The bleeding region itself was characterized by a loss of surface epithelium, marked hemorrhage in the underlying super-

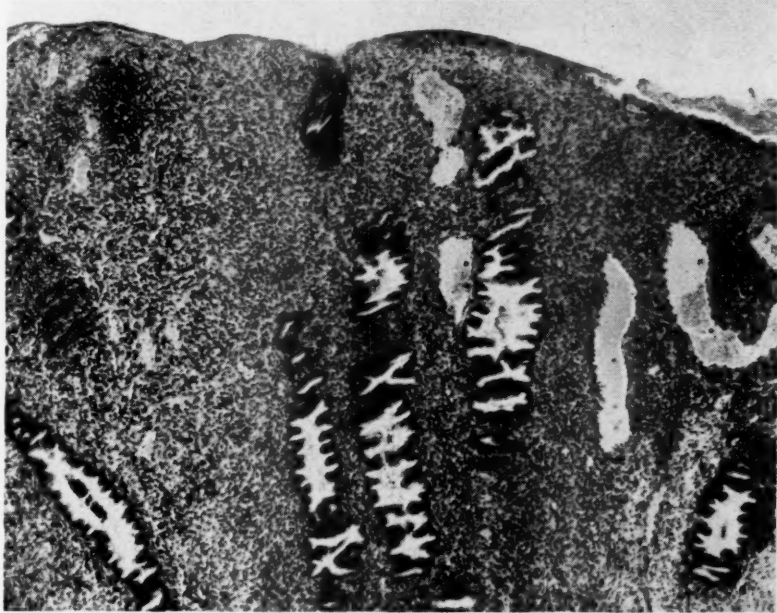
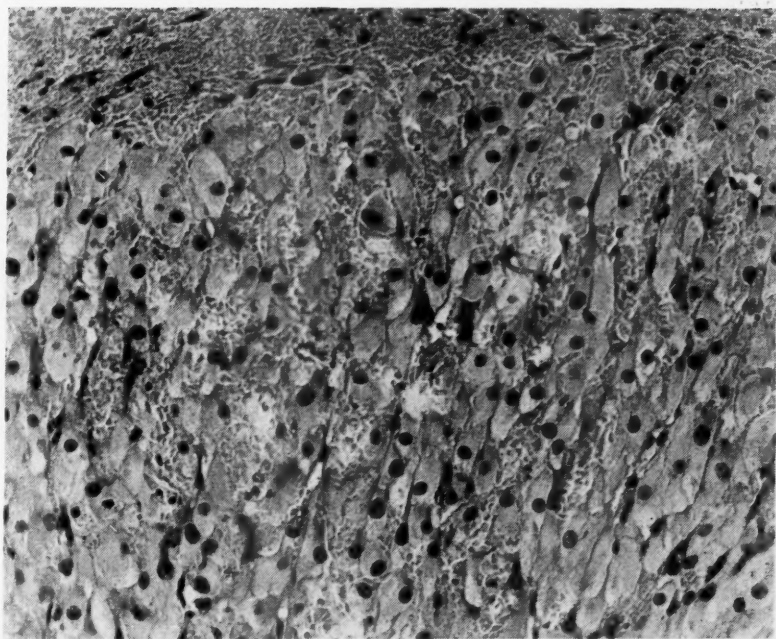


Fig. 19.—Specimen No. 375. The corpus luteum is young and is normal.

Fig. 20.—Specimen No. 375. This portion of the endometrium has responded to progesterone stimulation to a greater degree than the development of the corpus luteum (Fig. 19) would indicate. Involution and other changes incident to bleeding have occurred.

ficial stroma, and desquamation of tissue. Hemorrhage and tissue fragments projected into the cavity of the uterus. The actual loss of tissue was not great.

Interpretation: The corpus luteum was young and was consistent with a normal day 20 of the cycle. Chemical analyses of the corpus luteum indicated normal functional activity of a young corpus luteum of this histologic age.

Most of the endometrium was typical of an endometrium immediately prior to the onset of flow. It was of the type usually associated with a mature corpus luteum of greater age than the corpus luteum found here.

Bleeding was occurring from the endometrium, although the corpus luteum was young, and development was progressing normally. The involution, desquamation, and bleeding phenomena of the endometrium were similar to that observed in normal menstruation.

In this specimen the bleeding mechanism and endometrial tissue reaction seemed independent of the corpus luteum function or failure of function.

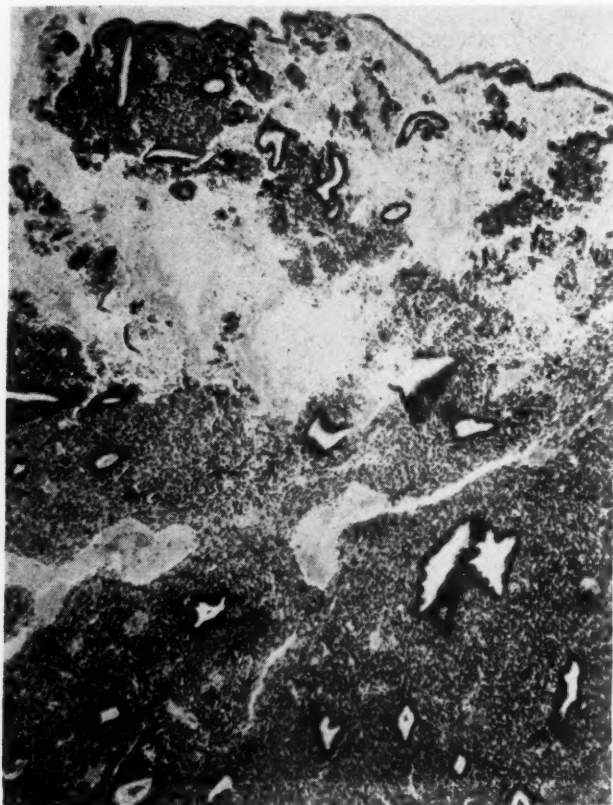


Fig. 21.—Specimen No. 375. Desquamation and bleeding are taking place in this localized region. Some of the glands evidence little secretory activity. The advanced degree of endometrium stimulation (Fig. 20), the involution, desquamation and bleeding are not consistent with the stage of development of the normal functioning corpus luteum (Fig. 19).

Discussion

In all of the specimens presented here the bleeding was from an endometrium which was progestational in type. A corpus luteum was present in the ovary in each instance. The relationships of the corpus luteum and the endometrium were not the same in all the specimens. There were two distinct types. In one group the corpus luteum appeared to vary from the normal. The abnormality consisted of a prolongation of life and function of the corpus luteum,

In response to the abnormal corpus luteum stimulation, the endometrium evidenced characteristic changes that have been described previously as "irregular shedding," "irregular regression," and "mixed type."

In the second group the corpus luteum and its functional activity appeared normal. The endometrium evidenced normal responses to the corpus luteum stimulation except in small localized regions. It was from these localized regions which have failed to respond that the bleeding occurred.

For the sake of convenience the specimens, accordingly, shall be grouped and discussed in that sequence.

Prolonged life of the corpus luteum in the form of a corpus luteum cyst has been frequently described. The life and function of the corpus luteum, however, may be prolonged without alteration of gross characteristics from the normal and without cyst formation. Direct evidence of this obtained by studies of corpora lutea themselves have been few, but evidence obtained by less direct means is quite conclusive. The evidence has been accumulated from endometrial specimens and biological assays of patients with functional uterine bleeding associated with a progestational type of endometrium. The endometrium in these instances is described as "irregular regression or shedding," and "mixed" type (Meyer;² Traut and Kuder;³ McKelvey;⁴ McKelvey and Samuels;⁷ and Jones⁶). That the life of the corpus luteum is prolonged in such instances is indicated by several studies. McKelvey and Samuels⁵ report the presence of pregnandiol in the urine of patients during the period of bleeding from such an endometrium. This indicates that progesterone secretion is continuing. Normally pregnandiol is not found during a bleeding phase. The endometrial gland cell and stromal tissue responses are those observed only as a result of progesterone stimulation. Holmstrom and McLennan⁷ produced the characteristic picture of "irregular shedding" with prolonged bleeding by giving injections of progesterone during the bleeding phase of the cycle of normally menstruating women, thus proving that prolonged secretion of progesterone can reproduce the endometrial changes and the prolonged bleeding.

In the present study microscopic characteristics of the corpus luteum during various stages of its prolonged life are described. These findings confirm the evidence noted above. The earliest phase in the cycle in which we observed undoubted prolongation of life of the corpus luteum was in a specimen (No. 335) obtained near the onset of bleeding. The duration of the bleeding period in this patient had in the past been prolonged to eight days. The corpus luteum (Fig. 1) was maintained in the vascular stage with but little evidence of degeneration on day 27. That bleeding was about to begin was indicated by the occurrence of involution of the endometrium (Fig. 2) and small local superficial regions of extravasation and desquamation (Fig. 3). Our study of many human specimens warrants the statement that such a corpus luteum as this is not normally found in this stage of the cycle. It also justifies the contention that such a corpus luteum as this would not regress immediately, but rather would degenerate over a period of several days.

Specimen No. 332 obtained on day 14 of bleeding showed such a picture. In some regions the granulosa lutein cells evidenced but few regressive changes

such as reduction in cell size associated with an increase of connective tissue throughout the layer (Fig. 5). The granulosa lutein cells appeared histologically similar to functioning cells. Other cells showed more regression, but none evidence more degeneration than was frequently observed in specimens obtained on day 1 to 5 of normal menstruation (Fig. 4). This "irregular" regression of the corpus luteum was an exaggeration of the normal. In normal menstruation on day 1 there were considerable variations in different portions of the same corpus luteum as well as in different corpora lutea (Brewer and Jones⁸). In normal menstruation, however, a corpus luteum is not maintained in such an intact state as this for fourteen days after the onset of bleeding. That the corpus luteum had continued to function is shown by the presence of some secretory glands in the endometrium (Fig. 7). Thus, the interpretation of function from the histologic picture of the granulosa lutein cells is accurate. Other glands in this still bleeding endometrium had regressed or had desquamated in part and were of the postmenstrual type (Fig. 6).

This specimen indicates without doubt that prolonged life and function of the corpus luteum does occur; that its regression, when it occurs, does so slowly and in an irregular way; and that it is a basic and fundamental part of so-called "irregular regression" of the endometrium and functional bleeding from a progestational endometrium. Irregular regression of the endometrium in reality is only an expression of the abnormality of the corpus luteum.

Another specimen, No. 334 obtained on day 8 of bleeding, had a corpus luteum which had persisted without much evidence of degeneration. It was large (1.5 cm.), was still vascularized, the granulosa lutein cells were intact, and the connective tissue throughout the layer and bordering the central cavity was scant. The endometrium in most regions contained glands that were secretory in type. Those portions of the glands that had not been desquamated were regressing. Desquamation seemed to have almost been completed. In other regions the endometrium was of the usual postmenstrual type, and was covered with surface epithelium. Regeneration had completed itself in some portions of the endometrium during the bleeding period, and it was more advanced than in the previous specimen. The prolonged life and function of the corpus luteum was apparent, since such findings as these are not present in normal menstruation. Irregular and prolonged regression of the endometrium occurred as a direct response to the irregular and prolonged degeneration of the corpus luteum. Prolonged bleeding is a natural sequence.

McKelvey⁴ observed that the longer the duration of bleeding the greater the variation in the endometrial pattern. Specimen No. 293 obtained on day 45 of bleeding confirms that observation. The endometrium in one portion was thin, was covered with intact surface epithelium, and contained glands that evidenced active secretory function (Fig. 9). The stroma was unusual in that there was a great amount of intercellular fluid. Other portions of the endometrium were desquamated, bleeding, had few glands, dense stroma, and contained many large blood sinuses (Fig. 9, arrow). Still other portions were intact, were covered with a newly regenerated epithelium, and had straight, nonsecretory, postmenstrual type of glands (Fig. 10). This region gave the

appearance of having sloughed and having regenerated completely, while other portions of the endometrium continued to bleed and desquamate, and still others remained in a state of secretory activity without slough or bleeding.

The associated corpus luteum was small, but it was typical of a postvascular stage from a histologic standpoint (Fig. 8). Although most of the granulosa lutein cells were small, they resembled functioning cells. That they still retained functional capacity was evidenced by the secretory character of the endometrium. The life of the corpus luteum in this instance had been prolonged in the regressive stage, and a slow irregular shedding of the endometrium had resulted. This specimen also clearly demonstrates the fact that recently regenerated endometrium is not able to respond to corpus luteum stimulation, and that a phase of growth is necessary prior to participation in mature function, namely, secretory activity and preparation for an implantation site.

Near the termination of a bleeding phase in this particular type of functional uterine bleeding there are certain typical findings. Specimen No. 265 obtained on day 11 of bleeding consisted of a small corpus luteum in which many of the granulosa lutein cells were degenerated, but a few granulosa lutein cells still retained their large size, even staining cytoplasm, intact cell membranes, and round or oval nuclei (Fig. 11). These cells, however, represent but an extremely small portion of the granulosa lutein layer. The picture in general is one of degeneration. The functional capacity of such a corpus luteum is nil. The life cycle of the corpus luteum, however, has obviously been prolonged, since cells such as those described are not present in corpora lutea of normal menstruation eleven days after the onset of bleeding.

The endometrium had been repaired in all except a few small regions, and was typical of a proliferative phase. A region still denuded of surface epithelium had the appearance by its surface contour of a zone in which healing would take place shortly (Fig. 12). The irregular shedding phase was represented in this late phase only by such still unhealed regions which still bled. The life of the corpus luteum had been prolonged, but regression was completed, and the endometrium had repaired itself and was developing for the next cycle. The endometrium not involved in the local bleeding regions had responded normally, and was consistent with a normal proliferative phase.

These specimens would indicate that abnormal or functional uterine bleeding does occur from an endometrium that evidences progestational characteristics. They indicate, as far as the pelvic organs are concerned, that the corpus luteum life cycle is altered from the normal in that its life and function are prolonged. As a result the endometrium is shed in an irregular way, a mixed pattern occurs, and the desquamating and bleeding phase is prolonged. As slough in one local region is completed, healing takes place, and that region of endometrium begins development, irrespective of the character of the other regions. Local variations in responses occur in the endometrium in normal menstrual cycles (Bartelmez;⁹ Brewer and Jones⁸), and it is only an exaggeration of this that is observed in this type of functional uterine bleeding. The corpus luteum in normal menstruation may, and frequently does, vary in dif-

ferent regions (Brewer and Jones⁸). Some cell regions evidence degeneration, and others do not. In functional uterine bleeding these variations may be exaggerated. Persistence of the corpus luteum in a certain phase for a longer time than usual, and prolongation of the degeneration phase seem to be the common phenomena observed in patients who have this particular type of abnormal bleeding from a progestational endometrium. The direct cause of the alteration of the life cycle is undoubtedly the pituitary, which in itself may or may not be the primary factor.

In this type of bleeding associated with irregular shedding of the endometrium, the bleeding and desquamation are similar to and are an exaggeration of the normal processes of menstruation.

Irregular shedding is not in itself an entity as advocated by some, but rather is only a part of a more general endocrine disturbance. The primary cause is not proved, but without doubt the corpus luteum and pituitary gland are involved.

The second group of corpus luteum endometrial relationships observed in patients with functional uterine bleeding from a progestational endometrium is composed of those specimens in which the corpus luteum cycle is normal, the endometrium responds normally, and the bleeding phenomena seem to be independent of the corpus luteum or the type of the endometrium.

The corpus luteum of Specimen No. 257 is of the postvascular early regression type (Brewer¹⁰), or the so-called bloom stage of other authors (Fig. 13). The endometrium, except in small regions, is consistent with this stage of life of the corpus luteum (Fig. 14). There is a normal relationship between these two tissues. This specimen was obtained on day 1 of bleeding, but a six weeks period of bleeding had just terminated seven days before the new bleeding started on the day of operation. Ovulation must have occurred during this previous period of bleeding, since the corpus luteum is older than seven days. In spite of the bleeding the normal mechanism of ovulation and corpus luteum development occurred, indicating that the hormonal balances and actions were within normal limits. The endometrium, for the most part, had developed and responded in the usual normal manner to corpus luteum stimulation. The relationship of these two tissues from the standpoint of secretory development and activity appeared normal. Portions of the endometrium, however, were bleeding. The bleeding was from large sinuses lying just beneath and parallel to the surface (Fig. 14). The surface epithelium was denuded, and active bleeding was in progress. The normal desquamation was lacking. The independence of this bleeding from the corpus luteum was apparent. The processes by which it was brought about were not determined.

Specimen No. 266 was obtained on the sixteenth day of continuous bleeding. The corpus luteum was young and from its histologic characteristics ovulation must have occurred during the sixteen-day period of continuous bleeding (Fig. 15). The major portion of the endometrium had responded to corpus luteum stimulation in a normal manner (Fig. 16). The early secretory type of glands and stromal reaction were consistent with the histologic picture of the corpus luteum. This suggests that the corpus luteum function corresponded

to its histologic development. One superficial region of the endometrium, however, was at variance with the general over-all picture (Fig. 16). The surface epithelium was lost; there was a scant superficial desquamation of the underlying stromal tissues; and blood and intercellular stromal fluid projected into the uterine cavity. This local region was at complete variance with the degree of development of the corpus luteum and endometrium. Since the corpus luteum and endometrium generally had reacted normally from an endocrine and tissue response standpoint, it can only be concluded that the localized bleeding was independent of corpus luteum control or function. This bleeding did not effect the normal response of the remainder of the endometrium. The explanation of the mechanism cannot be made, but its independence was apparent.

Specimen No. 273 was obtained on the sixtieth day of continuous bleeding. Ovulation in this specimen must have occurred during this period of bleeding, and the development of the corpus luteum progressed normally in spite of the bleeding. The corpus luteum was in the immediate postvascular stage (Fig. 17). That it was functioning was indicated by the histologic picture of the endometrium which showed progesterone stimulation. The development of secretory activity of the gland cells was less than would be anticipated normally, but this was probably due to the fact that the endometrial response was somewhat retarded due to recent regeneration. One region was denuded of surface epithelium, and slight bleeding was occurring (Fig. 18). There was scant desquamation of the tissue, and the depressed surface was quite regular. There was a complete independence of the tissue reaction in this region from the remainder of the endometrium which was normal. There was likewise no evidence that this region has any close relationship to the corpus luteum function, but rather it appeared completely independent. The bleeding seemed to be the result of some local fault in the endometrium, and appeared to be independent of corpus luteum function or failure of function.

That the bleeding may be a part of a mechanism that is independent of the ovary is not a new thought. It was stated by Bartelmez⁹ that "variations in the endometrium in menstruation point toward the relative independence from the ovary of the vascular control of the uterus." In a recent study of corpus luteum-endometrial relationships at or near the onset of normal menstruation, the impression was gained that the bleeding phenomena did not correlate well with the histology of the normal corpus luteum (Brewer and Jones⁸). Traut and Kuder³ were impressed with the independence that the mechanism of endometrial blood loss may show of the factors controlling tissue change. The second group of specimens reported here had endometrial tissue changes that are consistent with the histology and functional activity of the corpus luteum, but the bleeding is at variance and has no apparent relation with the corpus luteum. The bleeding in these specimens of the second group is not typical of normal menstrual slough and bleeding, but rather the bleeding seems to be from vascular sinuses without much tissue loss or local tissue reaction, such as involution, extravasation, and infiltration of leucocytes and lymphocytes. Hamblen¹¹ noted in cyclic bleeding associated with menorrhagia and a secretory type of endometrium that the bleeding in general was not characterized by tissue loss in the

endometrium as in normal menstruation. Jones⁶ observed normal premenstrual tissues in eight patients in whom active bleeding had been going on up to thirty-four days, and stated that apparently the bleeding was occurring from an endometrium which was not being shed to the extent that occurred in normal menstruation. This type of bleeding is exemplified by specimen No. 257. Watson¹² noted free bleeding from the vascular bed in instances associated with continued secretion of progesterone. Kurzrok¹³ observed that bleeding beginning at ovulation may continue up to menstruation, that the endometrium is in the secretory phase, and that the endometrium increases normally in development, irrespective of the continued bleeding. Our Specimens No. 257, No. 266, and No. 273 demonstrate this. Kurzrok felt that the factors responsible for the bleeding were not dependent upon the histologic type of the endometrium. We would like to go farther and say that in this particular type of functional uterine bleeding the factors responsible are not dependent upon either the histologic type of the endometrium or the corpus luteum.

From a study of these tissues, it is apparent that ovulation may occur during a period of abnormal bleeding, that corpus luteum development may progress normally, and that the endometrium may respond normally and continue to develop normally. If the bleeding were the result of abnormal endocrine factors, it is hard to explain why all these other normal tissue developments, both from a histologic and endocrine standpoint, should continue to maintain. The only possible conclusion is that the bleeding mechanism in such instances is independent of the function of the corpus luteum. That the factor responsible resides within the endometrium proper as Kurzrok suggested is entirely possible. That the endometrium cannot respond normally to normal stimulation may be a factor in the causation of this type of bleeding. This factor has not been given adequate consideration primarily because it is difficult to prove.

One specimen (No. 375) suggests that abnormal responses of the endometrium can be primary in causing functional bleeding in some instances. The specimen was obtained on day 20 of the cycle, yet abnormal bleeding had begun late in the day on day 19. At the time of operation, bleeding had been in progress for less than twenty-four hours, so this is termed a day 1 case of functional uterine bleeding. The corpus luteum is histologically normal and is in every way comparable to a young corpus luteum that might be obtained on day 20 of a normal twenty-eight day menstrual cycle (Fig. 19). That its function is normal was determined by chemical analysis of one-half of the corpus luteum (Weinhouse and Brewer¹⁴). The phospholipid and cholesterol ester values expressed in per cent of moist weight of tissue were respectively 1.38 and 0.11. These values are comparable with those obtained in corpora lutea of the same age of normal menstrual cycles. The phospholipids indicate functional activity of the tissue, and the low cholesterol ester values indicate that degeneration has not occurred, since these values are high during degeneration (1.25 in day 1 cases, Weinhouse and Brewer¹⁴). The endometrial responses, however, did not correspond in degree of development and activity to that of the corpus luteum. The glands in most regions were stimulated to a degree far greater than anticipated. Involution had occurred, and there was a super-

ficial extravasation of lymphocytes and leucocytes indicative of impending menstruation (Fig. 20). In one localized portion desquamation and bleeding had occurred (Fig. 21). In this region the glands were simple and showed little evidence of active or antecedent secretory activity. This may be the direct result of involution, or it is possible the gland cells did not adequately respond to stimulation. No other luteinized tissue was present in the ovaries. Both ovaries were removed, and careful search revealed none. The endometrium had not responded in the usual way to corpus luteum stimulation. The tissue changes incident to bleeding were similar to those observed in normal cycles. These characteristic changes, however, are usually found in association with a mature corpus luteum that evidences regression. Here the corpus luteum was young and, from a histologic and chemical analysis standpoint, was functioning normally. An explanation of this relationship between the corpus luteum and endometrium is difficult, since it does not correspond to anything that we have observed in abnormal or normal uterine bleeding. The abnormal reaction of the endometrial tissue in the presence of a normal corpus luteum suggests that in this instance the factor or factors that initiate bleeding reside within the uterus and may be independent of the corpus luteum.

Summary

Functional uterine bleeding may occur when a corpus luteum is present in the ovary. The endometrium in some instances may evidence irregular regression (Specimens 335, 332, 334, 293, and 265). The irregular regression is the result of prolonged life and function of the corpus luteum. The endometrial picture will vary, depending upon the rate and extent of regression of the corpus luteum. The bleeding which occurs seems to be an exaggeration of the normal bleeding processes observed in cyclic menstruation.

The corpus luteum in other instances may be histologically and functionally normal. The endometrium, except in small regions, responds normally. It is from these small regions that bleeding occurs. The bleeding in these instances is independent of the corpus luteum and of the remainder of the endometrium. The bleeding is unlike the usual normal menstrual bleeding. It is localized bleeding from blood sinuses with scant loss of endometrial tissues. During this type of bleeding ovulation can occur, corpus luteum development can progress normally, and the endometrium not involved in the bleeding can develop normally. (Specimens 257, 266, 273.) The phenomena that occur that produce the bleeding in such instances are not known. The explanation may reside in a local bleeding factor in the endometrium or in the local abnormality of response of the endometrium.

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Discussion

DR. M. E. DAVIS, Chicago, Ill.—It is not an easy matter to seek out bleeding points on the wide expanse of an endometrial surface and subject them to careful study.

No one can find fault with the histologic data presented. They have been accumulated by one thoroughly trained in the histologic anatomy and pathologic changes of the reproductive organs. The facts which Dr. Brewer presented are thoroughly reliable.

The physiologic interpretation of these findings, however, leaves room for many questions and, at least, a difference of opinion. It is difficult to accept a thesis which would cast doubt on many facts which we have considered as settled.

The normal hormonal control of the endometrium has been fairly well established. The growth of the endometrium, the development of the vascular mechanism, and bleeding are all the result of estrogenic stimulation. Bleeding is initiated by a sudden drop in the estrogen level, or perhaps by a change in the metabolism of this substance. That this is due to the direct action on the spiral arteries with the production of ischemia and necrosis is not known. If estrogens play the dominant role in the mechanism of normal bleeding, what is the function of progesterone? It is entirely possible that this hormone is responsible for progestational changes only. Thus, the edema of the stroma, the development of the decidual cells, the secretory changes in the glands, all necessary to normal nidation, are the result of progesterone.

If this thesis is correct, there is little difference between ovulatory and anovulatory bleeding. In the normal ovulatory cycle estrogens are supplied in the preovulatory phase by the growing follicle and the postovulatory phase by the corpus luteum. In anovulatory bleeding the estrogenic stimulation may be prolonged and variable, thereby resulting in irregular bleeding patterns. It is not necessary to postulate the presence of a bleeding factor to explain some of the discrepancies in these case histories. Deranged hormonal controls could explain most of the findings.

The cause of local areas of endometrial necrosis may well represent underlying local vascular changes. It is possible that the estrogenic influence may not extend to the entire vascular bed or that some areas are less sensitive to stimulation. It is likewise possible that such areas may continue to bleed for long periods of time.

Lastly, there are few studies correlating the histologic appearance of corpora lutea and their endocrinal function. The appearance of a corpus luteum may not be an accurate index of the endocrinal influence it exerts on the target organs. Much more data will have to be accumulated before we can answer many of the provocative questions raised by the essayist.

DR. EMIL NOVAK, Baltimore, Md.—Dr. Brewer's paper underlines the correctness of the statement so often made that bleeding can occur from any histologic type of endometrium. The type of endometrium with which his paper deals is certainly not to be compared in frequency with the anovulatory form of functional bleeding. The latter is due to an aberration of the anovulatory type of cycle, numerically much less common than the ovulatory, but occurring with especial frequency at those phases of menstrual life when functional bleeding is so often seen, i.e., puberty and adolescence on the one hand, and the premenopausal period on the other. This in itself is suggestive. The anovulatory cycle appears to be a more primitive, incomplete, and unstable one than the ovulatory.

Dr. Brewer's cases, however, appear to represent a subvariety of the ovulatory variety of bleeding, concerning whose mechanism we know very little. I do not believe that most

cases would show such areas as Dr. Brewer has shown in his slides, and in which the mechanism may involve some local factor in the endometrium as he himself suggests.

Since the spiral arteriolar system is so important in the production of normal menstrual bleeding, it has been suggested that a local vascular abnormality or disturbance may play a chief role in the production of the ovulatory type of bleeding. Dr. Reynolds has stated that spiral arterioles are completely absent in the endometrium of certain African monkeys which menstruate quite normally. There appears to be an innate bleeding propensity in the endometrium, this being histologically expressed in more elaborate form in the spiral arteriolar apparatus observed in most monkeys and all human females.

As to the local factor suggested by Dr. Brewer, I am more and more convinced that this must always be reckoned with in the interpretation of many endometrial lesions. Side by side, in the same endometrium, under the influence of the same hormonal factors, one may see an area of beautiful progestational appearance and one of Swiss-cheese hyperplasia, and other instances of localized variations in the sensity or refractoriness to the ovarian hormones might be cited.

DR. BREWER (Closing).—It seems to us that the endometrial responses have been neglected in the various manifestations and phenomena of uterine bleeding, and we feel that they are important. It is difficult to explain some of the bleeding phenomena on the basis of the endocrine function when the major portion of the endometrium has responded in a completely normal way. We feel that since these relationships are normal and the tissues are normal—and in the last specimens we had chemical analyses indicating that they were normal—the bleeding must be due to some other factor which is local in the endometrium. We do not believe all mechanisms are as yet explained.

ATYPICAL ENDOMETRIAL HYPERPLASIA SIMULATING ADENOCARCINOMA*

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(From the Department of Gynecology, Johns Hopkins Medical School)

THE purpose of this paper is to call attention to a group of benign hyperplastic lesions of the endometrium which may be and often have been mistaken for adenocarcinoma. While these lesions are actually hyperplastic in a general pathological sense, they are very different in their histologic characteristics from the ordinary type of benign endometrial hyperplasia. The latter term has come to have reference in gynecologic literature to the Swiss-cheese type of endometrium, characterized especially by disparity in the size of the glands, some being large and cystic, and some small, together with a rather abundant, compact stroma. The term, as first applied by Cullen, seemed appropriate for a lesion in which both epithelial and stromal elements exhibit hyperplasia. It does not apply to endometria which show only an occasional cystic gland, for this may be found in even a typical normal progestational endometrium, frequently in the basalis and not so infrequently in the functional layers.

For that matter, areas of Swiss-cheese endometrium of even considerable size may be found in otherwise normally functioning endometrium, representing what might be considered intraendometrial polyps made up of unripe endometrium similar in appearance to that making up most endometrial polyps growing from the surface. We mention these things simply to emphasize that the reaction of the endometrium to the ovarian hormones is not always the same in all its parts, just as its reaction is normally different at different endometrial levels.

The histologic appearance of any part of the endometrium is determined not only by the hormonal influence to which it is subjected, but also by its own degree of sensitivity or refractoriness to the hormones in question. The degree of maturity or immaturity, ripeness or unripeness of the endometrium, appears to be the most important factor in determining the degree of its receptivity to the ovarian hormones. In general it seems to be true that young, immature endometrium is highly responsive to the growth effect of estrogen and refractory to the differentiating hormone, progesterone. The reverse appears to be true of more mature endometrial elements, such as those normally found in the functionalis.

It is of interest that Schröder, who deserves the chief credit for the complete description of hyperplasia, as well as its cause and its relation to functional bleeding, selected exactly the same designation for this lesion as had Cullen

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many years earlier. At the outset, to avoid misconception of our paper, we would like to emphasize two points.

The histologic picture presented by the ordinary Swiss-cheese hyperplasia does not in the slightest degree resemble that of adenocarcinoma. Secondly, the ordinary hyperplasia as observed during reproductive life has no tendency toward malignant transformation. It is true that Meyer¹ has reported one or two instances of carcinoma occurring in association with such hyperplasia, but the rarity of observations, in a condition as common as hyperplasia, makes it seem certain that any association must be looked upon as coincidental. A number of authors (Novak and Yui,² Taylor³) believe that the endometrial hyperplasia not infrequently seen in women well beyond the menopause may play a predisposing role in the development of cancer, but we are not here concerned with this problem.

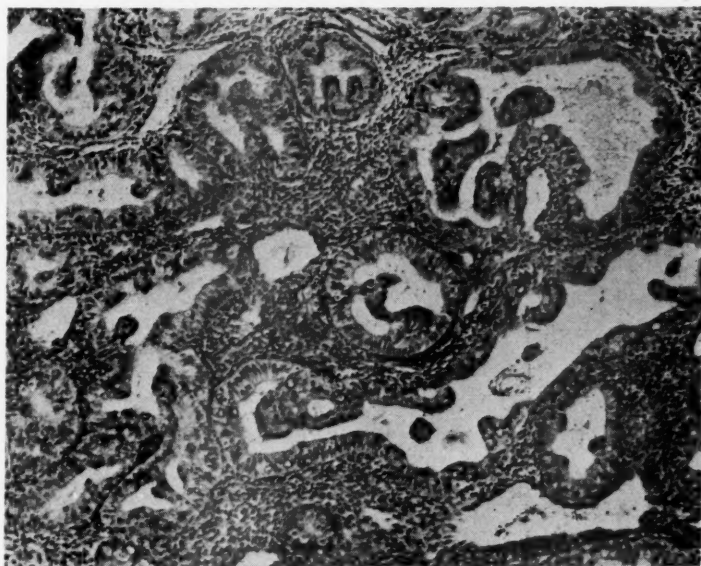


Fig. 1.—Patient, aged 49 years, had had x-ray induction of menopause four years previously. For some months before curettage the patient had taken 1 mg. stilbestrol daily for menopausal symptoms, followed by bleeding five days after withdrawal of drug. Picture shown above had been diagnosed adenocarcinoma, but was considered by us to be benign. Repetition of curettage four or five weeks later showed regression of endometrium to extreme senile atrophy (see Fig. 2).

We have been impressed with the fact that the simple type of Swiss-cheese hyperplasia does not represent the only abnormal endometrial pattern which may be produced by excessive or prolonged estrogen stimulation, either in the human female or in the experimental animal, and that these other growth patterns are often totally different in histological appearance from the Swiss-cheese type. The term hyperplasia, as used in gynecologic literature, has come to refer to the Swiss-cheese type, but the atypical forms are just as hyperplastic from a pathologic standpoint. This atypical hyperplasia may be fairly uniform throughout the endometrium, but more frequently the atypical lesion occurs in one or in many localized areas of an endometrium which otherwise presents an

obviously benign Swiss-cheese picture. Only two interpretations of these localized, cancerlike areas seem to offer themselves. One is that these often highly atypical areas actually represent multicentric carcinoma developing in benign Swiss-cheese hyperplasia. The other would be that these abnormal cancerlike areas represent different degrees or types of estrogen effect upon areas which respond differently to the same estrogen growth stimulus. This we believe to be the correct explanation, as we hope to show in this paper. This conclusion carries with it also the connotation that such areas are not histologically indicative of malignancy.

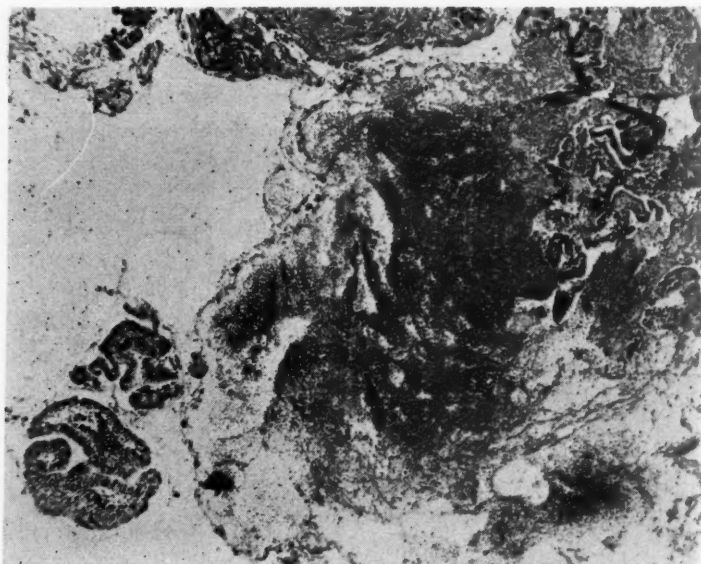


Fig. 2.—Extreme atrophy of endometrium, with no suggestion of carcinoma in same case as shown in Fig. 1. Only few fragments of senile endometrium obtained, picture showing chiefly blood.

A good illustration of the variations in the histologic effect produced by the same estrogenic agent is seen in the examination of the endometria of women who have been taking diethylstilbestrol, often in considerable dosage, continuously for inordinate lengths of time. No gynecologist need be told that the abuse of this drug, in itself a very valuable one, is a widespread evil, and that postmenopausal bleeding is a frequent result of such injudicious therapy of menopausal vasomotor symptoms. We have had the opportunity of examining a number of the endometria of such patients, and of noting that the hyperplastic effects of the drug vary greatly in degree and in character. While in some cases they are of mild degree and usually of benign Swiss-cheese character, in the occasional case they are very atypical, with such high degrees of adenomatous and proliferative activity that they may easily be mistaken for adenocarcinoma.

Fig. 1, for example, represents the endometrium of a postmenopausal woman who had been taking stilbestrol for many months and who developed postmenopausal bleeding which led the surgeon to do a diagnostic curettage. A di-

agnosis of adenocarcinoma was made by two competent general pathologists, and radical operation advised. The sections were sent to our laboratory for examination, and we interpreted them as benign. The suggestion was made that a repeat curettage be done in a month, the stilbestrol having of course already been discontinued. Fig. 2 shows that the endometrium had regressed to the normal postmenopausal pattern.

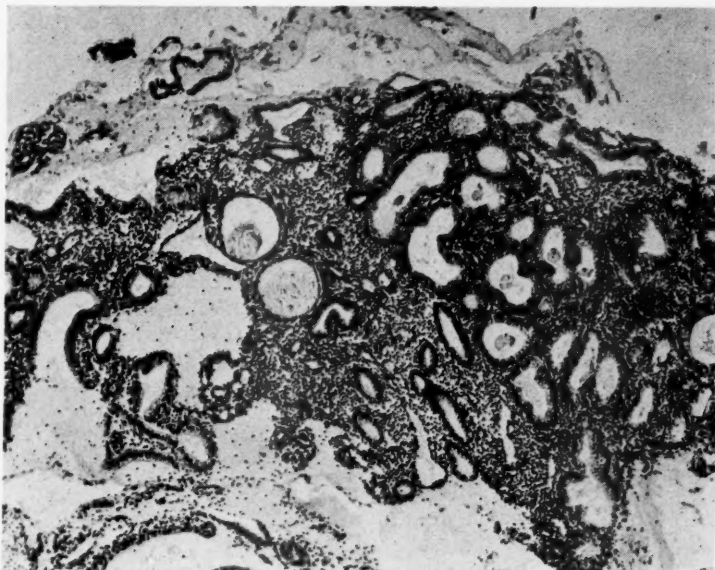


Fig. 3.—Very mild hyperplasia, not of typical Swiss-cheese type, and not at all suspicious of malignancy, in woman 55 years of age, treated with curettage and x-ray.



Fig. 4.—Adenomatous hyperplasia in woman 55 years of age, following previous excessive stilbestrol. This patient had a hysterectomy. Section is from near uterine cornu.

What are some of the atypical proliferative patterns which may lead to the incorrect diagnosis of carcinoma? They may be put down as follows: (1) increased number, crowding, and moderate atypicalness of the glands; (2) stratification, abnormal staining, and atypical morphology of the epithelium; and (3) the presence of squamous plaques in the walls of the glands, and occasionally on the surface.

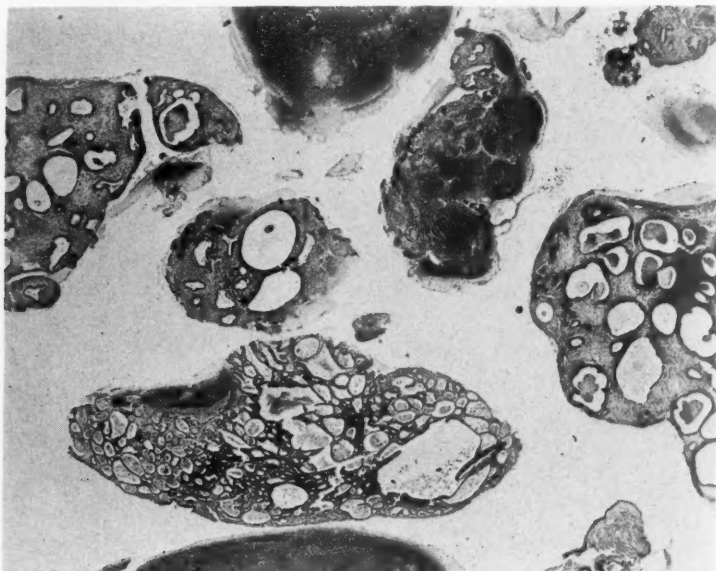


Fig. 5.—Adenomatous crowding of glands in small polyp in lower portion of picture, remainder of endometrium showing Swiss-cheese pattern. Patient was 62 years of age, and had had a postmenopausal hysterectomy.

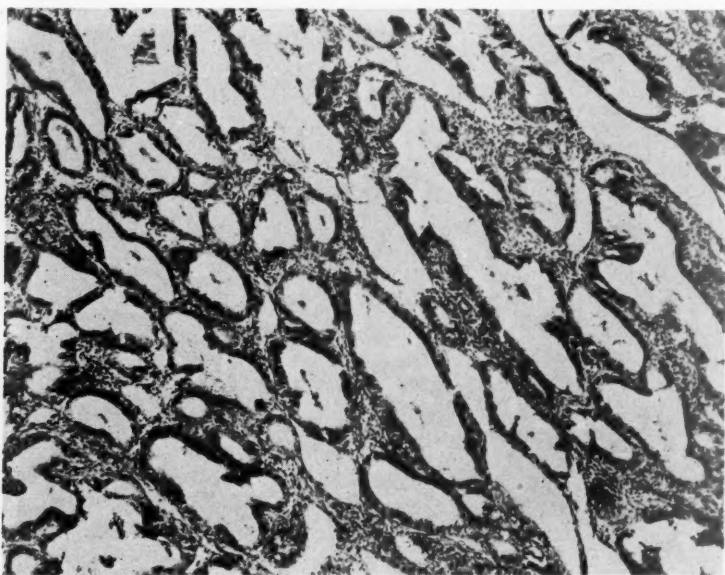


Fig. 6.—Markedly adenomatous picture in a woman 41 years of age, who had curettage followed by hysterectomy, without preliminary radiation. No gross lesion was found, and the patient was well two years later. We do not think this lesion was malignant.

1. In the ordinary Swiss-cheese type of endometrium the glands are scattered discretely in an abundant stroma. In the atypical forms of hyperplasia, the glands are greatly increased in number, with very little intervening stroma, and in such areas no cystic glands are likely to be seen. In some of these adenomatous areas the glands show comparatively little convolution, in others

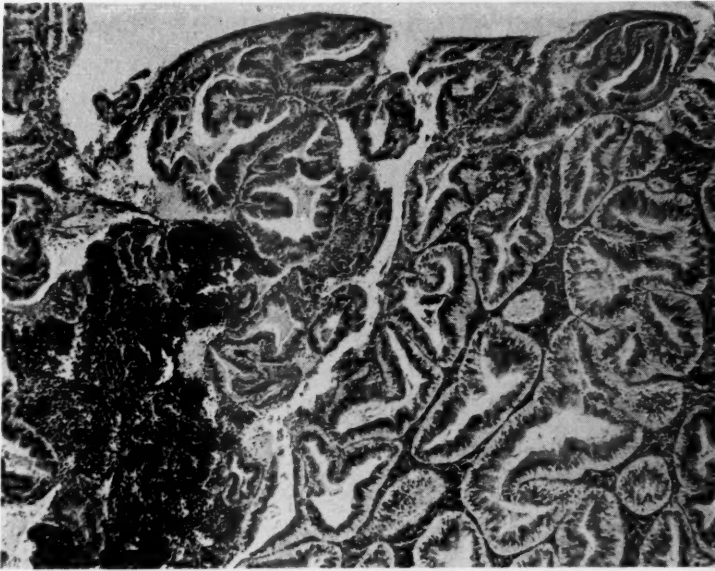


Fig. 7.—Pseudomalignant hyperplasia in woman 49 years of age, who had only curettage and x-ray induction of menopause one year previously. No bleeding since then. Note tall, well-differentiated epithelium with small needlelike nuclei.

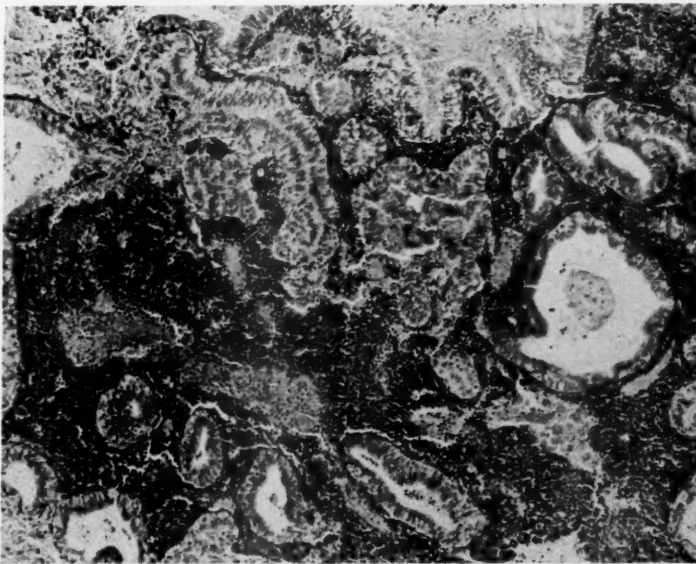


Fig. 8.—A relatively common finding in atypical hyperplasia is seen in the pale staining areas, often multiple, probably explained by the immaturity of the epithelium. This is not indicative of malignancy. The hysterectomy in this patient, aged 52 years, was probably unnecessary. There was no radiation. No gross lesion was found, and she is well one and one-half years after operation.

the gland pattern is as atypical as in many instances of adenocarcinoma. Marked adenoma-like crowding of the glands is especially common in endometrial polyps, which are usually made up of an immature type of endimetrium.

2. Even in clearly benign hyperplasia stratification of the gland epithelium is not uncommon, especially in the smaller noncystic glands. As a rule, however,

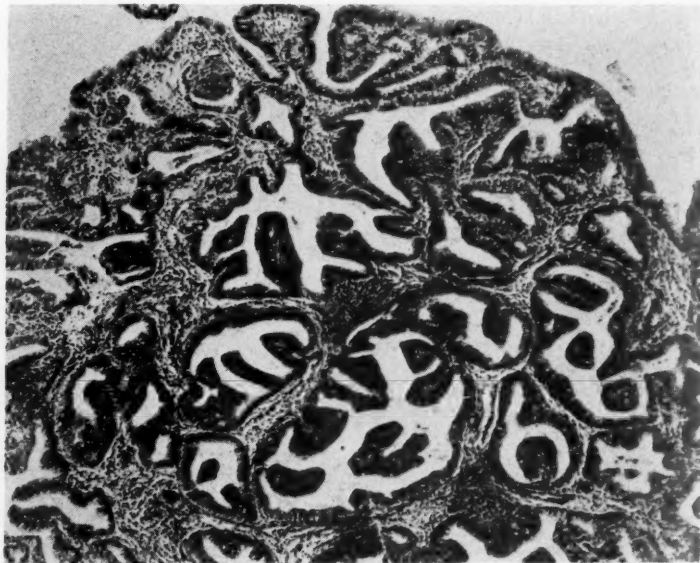


Fig. 9.—Patient aged 29 years had a hysterectomy without preliminary radiation. The removed uterus showed no lesion, and she is well two and one-half years after operation. While this lesion is certainly highly suspicious, and hysterectomy was justified, we are inclined to believe that the picture represents an atypical hyperplasia rather than adenocarcinoma.

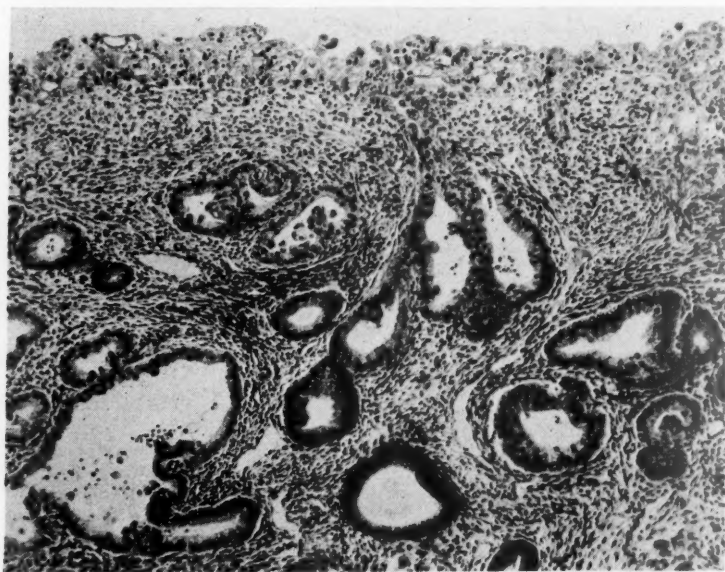


Fig. 10.—This patient, aged 49 years, had curettage followed by hysterectomy, which showed no gross lesion, and she was well when last heard from, ten years later. Note the peculiar syncytial-like metaplasia on surface, and in one or two of the glands.

not more than two layers of cells are seen. In the atypical variety such stratification is much more common and often extensive. The epithelial cells in both the typical and atypical forms of hyperplasia often show moderately large and dark-staining nuclei, but exceptions are noted in many of the atypical cases, in that the epithelium may be very tall, with small fusiform, sometimes almost needlelike nuclei. They are very uniform, with no suggestion of the nuclear hyperactivity characteristic of cancer.

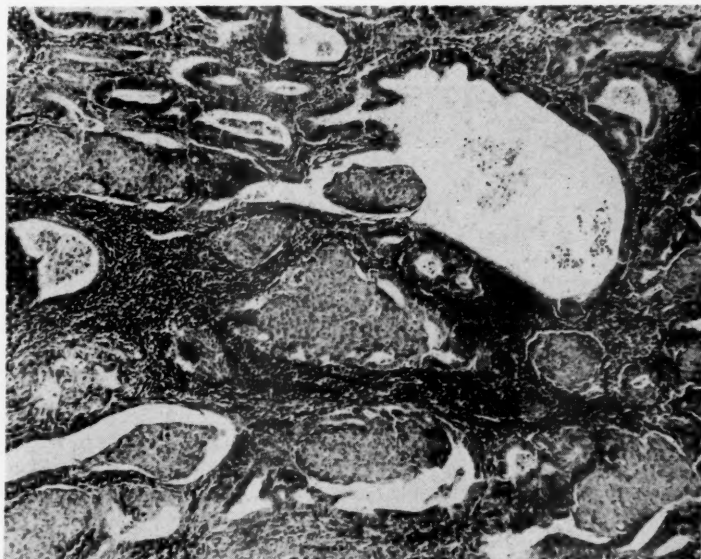


Fig. 11.—Extensive squamous metaplasia in an endometrium which otherwise shows a benign, Swiss cheese hyperplasia. Such lesions are often diagnosed as adenoacanthoma and treated as cancer. They are probably sufficiently suspicious to justify this plan, which was carried out in this patient. No preliminary radiation was used, and no gross lesion was found in the removed uterus. She was 35 years old, and was well nine years later.

Such areas often stand out very sharply from the surrounding endometrium because of their pale staining, which seems explainable only on the basis of the greater immaturity of the cells. Not all such light staining areas are lined by the type of epithelium above described. Some show epithelium which consists of two types of cells similar to those characterizing the tubal epithelium, even to the presence of cilia. Such areas are to be interpreted as instances of the segmental differentiation anomalies so often seen in the genital canal (proso-plasia or retroplasia), as described in a previous paper by one of the present authors.⁴ The occasional finding of typical endometrium in the tube is another instance of such differentiation anomalies. Finally, though rarely, the stratification of either the surface or gland epithelium in cases of atypical hyperplasia may assume a peculiar syncytium-like appearance, as described in the paper by Novak and Yui in 1936.²

3. Squamous plaques may be noted in either benign hyperplasia of the endometrium or in association with adenocarcinoma (adenoacanthoma), the latter more frequently than the former. Many cases of adenocarcinoma have thus been wrongly interpreted as combined squamous cell and adenocarcinoma, but

the squamous plaques in themselves show no histological evidence of malignancy. A number of studies of these squamous nodules have been made (Polano, Sitzenfrey, Meyer, Engelhorn) and the prevailing viewpoint is that they have their origin from certain indifferent cell elements beneath the columnar cells. These indifferent cells possess differentiating potentialities which may result in the formation of small squamous nodules which at times push into the gland lumen in a glomerular-like fashion, as Meyer pointed out.⁵ The overlying gland epithelium may be displaced, while in other cases the squamous growth pushes out into the surrounding stroma, producing plaques of considerable size.

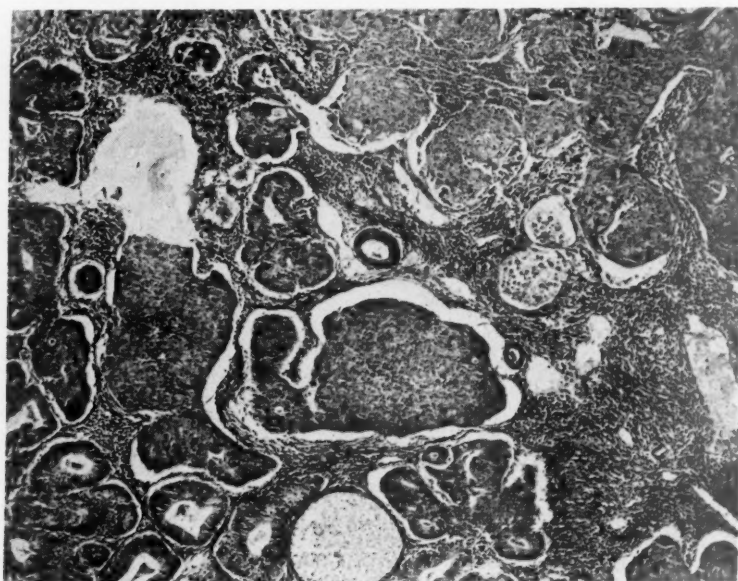


Fig. 12.—Extreme squamous metaplasia, with rather proliferative hyperplasia in a few areas of an endometrium which in most parts was of Swiss-cheese type. The patient, aged 55 years, not postmenopausal, was curetted, with no radiation or hysterectomy. No symptoms two years later.

When such squamous areas occur in a benign hyperplastic endometrium, as they occasionally do, they bring about a picture which is apt to appear more wicked histologically than it is clinically. At any rate, they are not in themselves to be looked upon as evidence of malignancy. It is on the characteristics of the gland elements that one should base such a diagnosis. It is our belief that a diagnosis of adenoacanthoma is not infrequently made in cases of benign hyperplasia associated with such squamous cell islands.

All the changes described above were described in papers by Hintze⁶ and Meyer,¹ both emanating from Meyer's laboratory. In all of the twenty-four cases reported by Hintze, there was no other treatment than curettage, and a follow-up of these cases revealed no evidence of subsequent carcinoma in any of them. A similar small group were described by Novak and Yui in 1936, and in a very recent paper by Corscaden and Gusberg,⁷ a number of illustrations portray lesions of this general character, the authors interpreting most of them as atypical carcinomalike hyperplasia rather than actually malignant. A study

of these photomicrographs leads us to believe that they are correct in making such an interpretation. This about exhausts the literature of the subject, so far as we can learn, in so far as human observations are concerned.

In the realm of experimental studies of estrogen stimulation upon the lower animal, there is a large amount of evidence to indicate that all gradations of abnormal growth effect may be produced in the endometrium, with often just such atypical hyperplastic and canceroid changes as we have been discussing. The most recent and most provocative study of this sort is that made in 1944 by Crossen and Loeb,⁸ who describe stratification of the epithelium, squamous metaplasia, and papillary changes in both the surface and gland epithelium. The lesions illustrated in their paper are quite like those which we have pictured in this paper, though no actually cancerous lesions were produced. They draw the same conclusions which have been impressed upon us as to the individual nature and degree of the responsiveness of endometrial tissue to estrogenic stimulation.

Material for Study

The material forming the immediate basis for this study consists of a group of cases which show atypical hyperplastic changes which might readily be mistaken for adenocarcinoma, and which, as a matter of fact, were actually so diagnosed in many instances. These cases were selected from a considerably larger group exhibiting less pronounced atypical pictures which few would interpret as malignant. The question naturally arises as to the criteria on which we have decided that the lesions in question are not actually malignant. These will be apparent from the grouping which we have adopted for the cases with these histologically questionable characteristics.

Group I. Cases receiving no treatment except curettage, or curettage plus radiologic induction of the menopause.—

If a woman is submitted to diagnostic curettage for uterine bleeding, we feel it entirely safe to assume in retrospect that the endometrial lesion was benign if she remains perfectly well for a term of years with no further treatment, or with no other treatment than x-ray or radium induction of the menopause, in a dosage which no one would consider adequate for the cure of carcinoma.

In this group we place eighteen of our cases, all showing histologic changes, sometimes diffuse and sometimes localized, which might easily have been mistaken for carcinoma. Sometimes the pseudomalignant picture occurred only in a single area, sometimes such confusing areas were multiple.

Eight of these eighteen cases had curettage alone, with no subsequent radiotherapy, and no further operative procedure. One of these is of special interest because the bleeding followed excessive diethylstilbestrol therapy in a woman 49 years of age, who four years previously had had x-ray induction of the menopause. This case has already been alluded to, and is illustrated in Figs. 1 and 2. The ages of the other patients in this group were 18, 21, 30, 33, 44, 49, 53, and 55 years. Only the one patient mentioned above was postmenopausal. This age distribution in itself is very different from that of adenocarcinoma, and this point we shall discuss later in this paper.

All eight of these patients have remained well for periods of from 1 to 21 years after the curettage. The 21-year-old patient in this series was delivered of twins sixteen years after the curettage. Another one of these patients is of special interest in that she remained well for fifteen years following simple

curettage, but then returned to this hospital with an adenocarcinoma which was treated by hysterectomy, preceded by radiation. This case perhaps is illustrative of the view, supported by the statistical studies of Corscaden and Gusberg,⁷ and Randall,⁸ that patients who have had menopausal functional bleeding have three and one-half times as great a chance as other women developing adenocarcinoma in later life.

As will be noted, even comparatively young patients may at times reveal these histologically disturbing pictures, as strikingly shown in one of the cases of this group. Because of excessive bleeding, this patient was curetted at the age of 18 years. A diagnosis of adenocarcinoma was made, and this was confirmed by one of the leading pathologists of the country. She was referred to one of us (E. N.) for further management. It was our opinion that the slide (Fig. 13) represented an atypical but benign hyperplasia. There had been no further abnormal bleeding, and no further treatment, organotherapeutic or otherwise, was considered necessary. The patient was later married and experienced a normal full-term delivery. In 1943 she was operated upon for the removal of a large dermoid cyst of the left ovary. In 1946 she was referred back to us because of a tumor, about the size of an orange, in the remaining ovary, and another large dermoid was removed, together with the uterus. The endometrium was entirely normal. Figs. 3 and 7 are further good examples of the atypical hyperplastic pictures encountered in this group of cases.

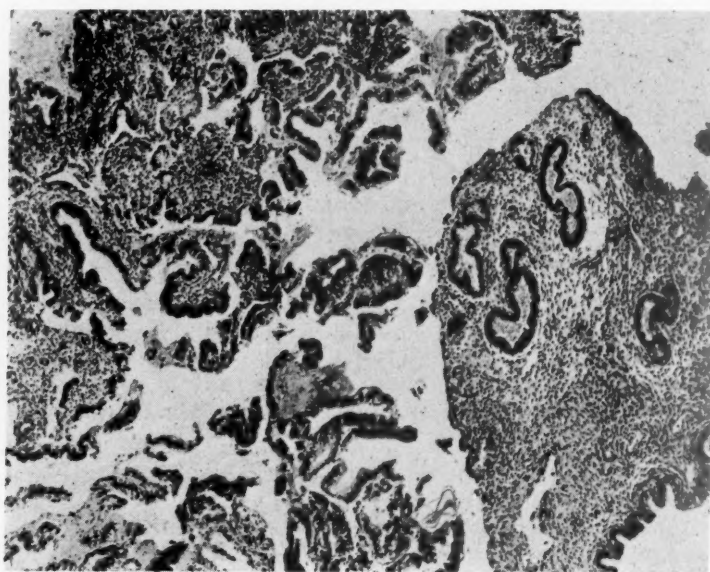


Fig. 13.—Endometrium of a girl 18 years of age, with moderate proliferative activity, but diagnosed as Grade I adenocarcinoma by a leading pathologist. No treatment after curettage, and patient well many years later.

The remaining ten cases of this very conservatively treated group received sterilization doses of either x-ray or radium. We have not been able to secure a follow-up of two of the older patients in this group, but the remainder have remained well, with no evidence of subsequent adenocarcinoma. These patients varied in age from 30 to 57 years.

Group II. Atypical hyperplasia, with subsequent hysterectomy, without preliminary radiation.—

In the ordinary case of adenocarcinoma, even after preliminary curettage, one expects, if the patient has not had preoperative radium, to find some gross

evidence of the cancer lesion when the removed uterus is opened. We appreciate that there are exceptions to this rule, as in the case of very small lesions, usually polypoid, which might have been entirely removed with the curette. Such cases, however, are relatively rare. Moreover, of the twenty-six cases which we have placed in this second group, all but one showed extensive areas in the endometrium of the removed uterus quite similar to the atypical lesions in the curettings. And yet, with one exception, there was no suggestion of a gross lesion. In view of the widespread microscopic changes, the absence of any gross lesion seems to us almost incompatible with the diagnosis of malignancy. In only one case was there a "small projection" on the endometrium, but this showed no microscopic suggestions of adenocarcinoma.

The atypical hyperplastic changes seen in this group of cases were often of a much more pronounced grade than those noted in our first group, and the simulation of cancer therefore much more perfect than in the latter. In many of these cases there was a difference of opinion among the pathologists of our group as to whether or not these lesions should be diagnosed as adenocarcinoma.



Fig. 14.—Endometrium of a woman 47 years of age, who had hysterectomy without preliminary radiation following the curetting. No gross lesion, and patient was well three and one-half years later. It was in this case that Josef Halban made the comment quoted in the text, "Nicht Karzinom, aber besser heraus!"

It is of interest to note that it was an examination of the sections from one of these cases (Fig. 14) that inspired the late Josef Halban on a visit to our laboratory to make the comment which we have so often quoted, "Nicht Karzinom, aber besser heraus!" This, as a matter of fact, has been our policy in this group of cases, and we believe it to be the safe one, even though such a retrospective study as this makes us feel that in these lesions the decisive cancer change had not occurred, and that these patients would probably have been cured by radiotherapeutic induction of the menopause.

The ages of these twenty-six patients varied from 29 to 66 years, distributed as follows: 29 years, 2; 35 years, 2; 37 years, 38 years; 39 years; 40 years; 41 years, 2; 43 years; 47 years; 48 years, 2; 49 years, 2; 52 years, 2; 56 years; 59 years; 62 years; and 66 years. In four patients having their source in outside clinics, the ages could not be accurately ascertained. It may be noted that

only three of these patients had passed the menopause. One of these, aged 59 years, had ceased menstruating five years previously, and in her case, the bleeding and the hyperplasia were obviously the result of injudicious stilbestrol therapy. One patient 62 years of age had had her menopause twenty years previously, and one 66 years of age, ten years before. It thus seems that postmenopausal hyperplasia may at times assume an atypical form, but that the great majority of such lesions are encountered while the ovaries are still functioning, and probably overfunctioning in the sense of producing a relative estrogen excess. This fact should make us suspect that the endometrial lesion is an estrogen-induced growth effect rather than a neoplasm.

Equally suggestive is the fact that only three of the twenty-six cases were postmenopausal. Such an age incidence is totally different from that of adenocarcinoma, which in approximately three-fourths of cases is a postmenopausal disease.

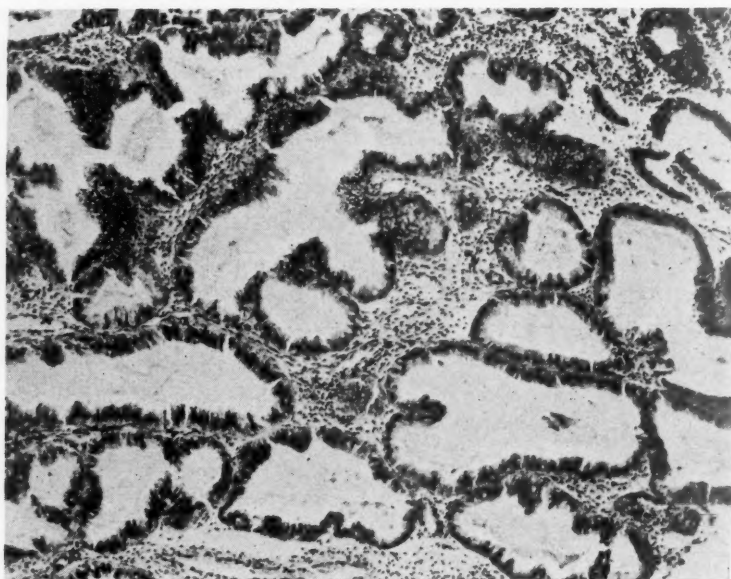


Fig. 15.—Another field in the endometrium shown in Fig. 13.

A follow-up of these cases was possible in all except six, most of which came from outside clinics. With three exceptions, all the cases date back more than three years, and every one of the twenty cases has remained well for periods varying from one to many years. It would be difficult to believe that such results could be achieved with actual carcinoma.

In some respects this group of endometrial lesions seems comparable to the so-called preinvasive carcinoma of the cervix, which likewise is clinically benign in the genuinely preinvasive phase. In at least some of our cases, the pseudomalignant change affected only the basal layer, while the overlying more superficial endometrium was fairly normal. Even where the changes were more diffuse, they were more pronounced in the basal layer, suggesting an abnormally exaggerated growth effect rather than a neoplasm. Moreover, there was an absence of the necrosis one would expect to find in carcinoma of corresponding extensiveness.

There was in no case any evidence of invasiveness, in the sense of penetration of the basement membrane or of myometrial involvement. It is true that it

is not always as easy to demonstrate invasiveness in undoubted adenocarcinoma of the endometrium as in the epidermoid carcinomas of the cervix, even though one may feel sure, from the occurrence of the metastases and other malignant characteristics, that invasive penetration into the lymphatics unquestionably occurs.

This leaves for final consideration the study of individual cell changes as a possible aid in the separation of benign and malignant lesions which, in so far as general architecture are concerned, seem to show no very striking differences.

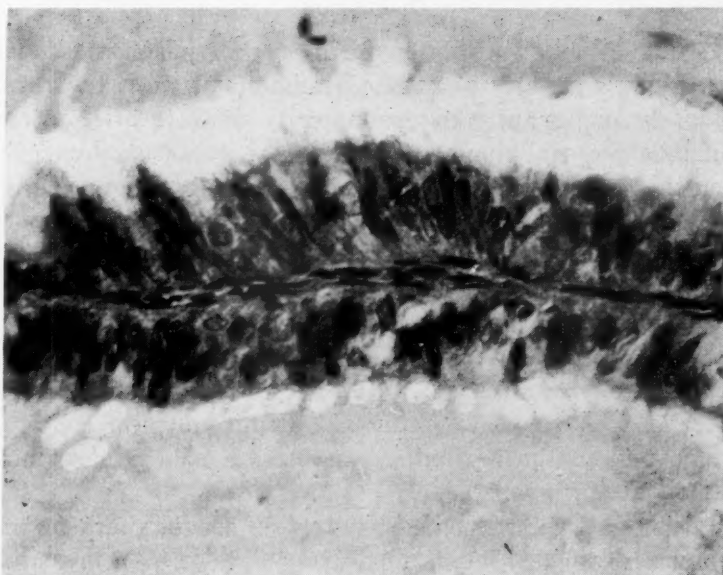


Fig. 16.—High power of the epithelium in two adjoining glands of case shown in Figs. 13 and 14. The epithelium is tall, pseudostratified, and the nuclei are comparatively small, long, and narrow, with no evidence of undue activity.

In at least some cases, the character of the individual cells would seem to be a reliable criterion, but in others it may be precarious. In some of the atypical hyperplastic cases the epithelium may show striking stratification, but the cells are tall, very narrow, with long, almost needlelike nuclei, with no sign of over-activity, and quite small in relation to the cell as a whole. In others the epithelium, as has already been mentioned, shows no stratification, no nuclear over-activity, and may resemble tubal epithelium. However, even in very benign hyperplasia of the Swiss-cheese type, the nuclei are at least moderately large and stain rather heavily with hematoxylin. Mitoses are of little differential value, since they are just as likely to be seen in benign hyperplasia as in adenocarcinoma.

While such cell study is thus of value in certain cases, it will leave the pathologist still uncertain in others, and we repeat that in the present state of our knowledge these genuinely doubtful cases should be treated as carcinoma.

In addition to the two groups described above, we have studied a third which we do not wish to submit as evidence to support our thesis, but which has revealed at least suggestive information along this line. During recent years, irradiation has preceded hysterectomy for adenocarcinoma in our clinic, as in most others. On re-examining the original curettings on which the diagnosis was made, we have encountered twelve patients in which the lesion is of the borderline group we have been discussing. In none of these was there any evi-

dence of carcinoma, either gross or microscopic, in the uterus after its removal. Our experience, like that of most others, has been that residual carcinoma can be expected in something like 50 per cent of carcinoma after presumably adequate intracavitary radiation. Either the radium in these cases was extraordinarily effective, or at least some of these were not malignant. In at least seven of the cases a review of the original sections shows lesions which we feel sure are benign, as in our Group 1 cases. In the other five they are of such suspicious type, like our Group 2 cases, that certainly the radical treatment employed was fully justified.

Discussion

In the study of any very large number of hyperplastic endometria one will encounter every possible histologic gradation between the frankly benign and the obviously malignant. In the majority of cases of adenocarcinoma of the endometrium the malignancy arises in a normal, nonhyperplastic endometrium, and the contrast between the benign and the malignant area is usually clear enough. But the atypical hyperplastic endometria being discussed in this paper may present difficulties of diagnosis.

The fact that the histologic transition between the benign and the malignant lesions is marked by almost insensible transitions does not of course mean that these gradations indicate the gradual transformation of a benign to a malignant lesion. The important consideration is that the irreversible somatic mutation which transforms a normal epithelial cell into a cancer cell is probably of short duration, and in the beginning cannot as a rule be determined by any histological method now available.

Comparatively soon it may engender certain cruder characteristics, such as obvious epithelial dedifferentiation, nuclear changes or even invasiveness, which make the distinction easy. But other common microscopic characteristics of adenocarcinoma are no less marked, and sometimes more so, in certain of these atypical hyperplastic processes than in the actually malignant one. It is another way of reiterating what most pathologists have always emphasized, that a lesion either is or is not a cancer, but that in individual cases it is simply impossible to make the decision by microscopic examination.

After all, the decision as to whether or not a given lesion is malignant or benign could best be made by the patient herself, were we to let her unfold her own story to recovery or to ultimate death. But we cannot use the human patient as a laboratory experimental animal. We must therefore do our best to separate these atypical lesions into two groups: (1) one in which, in spite of certain atypical characteristics, we can be quite certain that cure can be effected by simple conservative treatment, thus avoiding extensive surgery, which is not without hazard, and also imposes on the patient the cloud of future uncertainty which is the inevitable lot of every cancer patient; (2) the group in which the possibility of already existing cancer cannot be eliminated, and in which conservative treatment might dangerously delay adequate cancer therapy.

We are convinced that every case in our Group 1 was nonmalignant, and we would not hesitate to employ conservative methods in the type of endometrial lesions found in this group. We are unorthodox enough to feel that all or nearly all of the lesions described in our Group 2 patients were also not malignant,

and yet we are convinced that such pictures are very often interpreted as adenocarcinoma. As a matter of fact there are few of us who would have the courage to withhold radical treatment in such cases. In these genuinely uncertain cases we ourselves practice this plan, although the time will probably come when we shall have available some more precise means of sifting out the benign lesions from those in which the irrevocable cancer mutation has occurred.

The fact that forty-four instances of these questionable lesions have been revealed by a survey of our own material which is not by any means exhaustive leads us to believe that in the aggregate they are numerous enough to have some vitiating influence on cancer statistics. Mistakes in pathologic diagnosis are of course inevitable in all fields of pathology, but we believe that in the endometrium, as in the breast, such misinterpretations are disproportionately common because these organs are under the physiological influence of estrogen. The ability of estrogen to produce pseudoneoplastic lesions in both the uterus and the breast has been abundantly established by experimental studies, and we believe that the lesions we have described in this paper belong to this category.

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Discussion

DR. WILLARD COOKE, Galveston, Texas.—Dr. Novak's paper indicates very clearly the necessity for the development not only of specially trained gynecologic pathologists, but of pathologically skilled clinicians. Under ideal conditions the material removed in the operating room should pass immediately to the laboratories of the clinical department in order that significant tissues may be selected in the light of clinical knowledge and curiosity, and may be blocked and cut in the most effective directions. This is, of course, impossible in the case of the private practitioner and, unfortunately, in many schools. It is, however, quite possible, at almost no cost, to have duplicate slides made by the pathologist for immediate study by the clinician—a procedure which should be universal.

In regard to the subject of Dr. Novak's paper, there are two points which require consideration. We may accept as a fact that the endometrial response to the cyclic hormonal stimuli is not always uniform either in degree or in timing. The assumption, however, that atypical localized changes in the endometrium are due to variations in hormonal supply, particularly if we restrict to a single hormone, must in our present state of ignorance in regard to the actions of these hormones, remain an assumption only. The fact that all of Dr. Novak's cases occurred in sexually active patients except for the single postmenopausal patient under artificial estrogenic therapy is suggestive. Yet, while I had not time for a review of our material, I have the definite impression that we have encountered lesions of the types described in uteri removed (for prolapse, etc.) from elderly, asymptomatic patients. Many years ago, upon encountering such lesions, I classified them as subsurface, sessile, or pedunculated adenomas. While we all recognize the grossly proliferative varieties of endometrial hyperplasia, I find it difficult to conceive of a single, massive definitely pedunculated papillary growth with a typical stroma and vascular distribution—occurring in the midst of an endo-

metrium either totally atrophic or undergoing perfectly normal cyclic changes without evidence of hyperplasia—as the result of a localized selective estrogenic effect. Similarly, I find it easier to conceive of histologically identical glandular formations as adenomata of independent unknown origin. This is particularly true if such lesions occur in otherwise clinically and histologically normal endometria—a condition which is not very rare.

The only rational basis for the selection of treatment in any case lies in the knowledge of the comparative ultimate risk to the patient of the various possible therapeutic measures: in the present instance, curettage plus observation, radiation, hysterectomy. We have a fairly clear idea of the risks attached to each of these three procedures per se. If further extensive study of these lesions determines their potential for immediate or remote malignancy, our rationalism will be greatly advanced. For the present, however, eradication is indicated when definite uncertainty exists.

DR. GEORGE GARDNER, Chicago, Ill.—Once more Dr. Novak, in collaboration with Dr. Rutledge, has selected a topic for his presentation which is vitally interesting. In support of his thesis he has cited forty-four pertinent cases from the files of the Johns Hopkins Laboratory of Gynecologic Pathology. But, so far as I can ascertain, their division into two groups is based essentially on the treatment given. The first group was subjected to curettage with or without radiation castration; in the second, the uterus was removed and radiation was not employed. Are you not impressed that the method of treatment is an unusual criterion for separating atypical hyperplasias into those that are benign with certainty, and those which are probably benign? Dr. Novak, we regret, has failed to describe the details of histologic differences between these two groups of endometria.

The term hyperplasia denotes an increase in the bulk of a structure, due to an increase in the number of its component parts. Consequently, in the endometrium there is a *physiologic hyperplasia* which occurs during the proliferative phase of each normal menstrual cycle. Although all of us are conversant with the classical picture of full-blown pathologic hyperplasia of the endometrium, where there is an abnormal proliferation and increase in both stromal and gland elements, each of us has great difficulty, in fact finds it practically impossible to define those features which determine the exact transition from physiologic to pathologic hyperplasia. Furthermore, we recognize that the gland and stromal elements do not always respond equally to the growth impulse; as a result many endometria evidencing pathologic hyperplasia reveal the atypical glandular features which Dr. Novak has again brought to our attention, i.e., instances where gland elements have proliferated more actively than stroma cells and reveal (1) increased number, crowding, and moderate atypicalness of the glands; (2) stratification, abnormal staining, and atypical morphology of the epithelium; and (3) the presence of squamous plaques in the walls of the glands, and occasionally on the surface. I hasten to add that the more prompt the fixation of tissues in a proper fixative, such as Bouin's fluid, and the more skilled the preparation of slides, the more frequently is one likely to see these atypical features in endometrial glands.

On the other hand, we are surprised that Dr. Novak did not comment on specimens in which there was an unusual response by stroma cells, because in some atypical hyperplasias they may manifest predecidual changes. Neither did he comment on the effect of infection per se on the pattern and appearance of endometrial glands, although in one of his slides there is marked leucocytic infiltration. Also we question his statement that a tubal type of epithelium in the endometrium is an abnormality; some authorities, Bartelmez for example, recognize the presence of ciliated cells interspersed among "secretory" cells in practically all normal endometria.

Finally, we come to the crux of the problem. Is it possible, with a high degree of accuracy, to differentiate histologically between atypical glandular hyperplasia and early adenocarcinoma of the endometrium? Each of us is constantly being confronted with this problem and all of us are confused; fortunately for the patients we have misdiagnosed many more benign cases as cancer, than cancers as benign hyperplasias. But we still have our problem with us because this charming presentation by Dr. Novak has in no way defined the criteria for accurately cataloguing all questionable endometria. We must continue, as

we have in the past, believing that certain ones are benign, fearing that others are malignant and treating each one according to the dictates of our changing knowledge. Apparently we must wait a while longer for an elucidation of those features which make for certainty in the diagnosis of these atypical cases, because Dr. Novak has not yet given us the answer.

DR. SUBODH MITRA, Calcutta, India.—I would like to know whether it is possible to find out more about the preinvasive phase of adenocarcinoma of the body of the uterus similar to the condition Dr. Novak has found in the endocervix; and whether the second slide which he showed, and some of the later ones, come under this phase of cancer of the body?

DR. NOVAK (Closing).—To enlighten Dr. Gardner as to the method of selecting our material, I may say that the point of departure was the study of a large number of slides of cases which had been diagnosed as hyperplasia or adenocarcinoma, but in which we knew nothing as to the clinical histories. When we sifted out the cases we were gratified to find that those in which the slides showed lesions which we thought to be benign fell into the groups described in our paper, in which the clinical evidence was either convincing or highly probable that they were in truth benign.

I do not think that any pathologist would invoke the factors of defective fixation or infection in the explanation of such lesions as we have shown in these slides. The pictures which one sees with defective fixation are totally different and usually easily recognizable, while the lesions of chronic endometritis due to infection are dominantly interstitial, with usually little or no epithelial change, even with intense chronic inflammation.

Finally, as to the advantages of studying cases of this general type, these appear to us fairly clear. With many of the milder forms of atypical hyperplasia, there should be no hesitation in excluding adenocarcinoma. With the more pronounced cases, in which even a skilled gynecologic pathologist cannot be sure, the study of a large number of cases, perhaps in many laboratories, may show that all remain well and that they reveal no gross lesion in the uterus. If these findings could be established in a very large number of cases, the evidence would seem clear that they are not malignant, but that they represent an exaggerated local growth effect of estrogen, as we believe them to be. And yet nothing is more certain than the fact that innumerable cases of this sort have been and are being diagnosed as adenocarcinoma in the laboratories of this country.

At the Section meeting in Atlantic City last week, the distinguished foreign guest, Dr. Julius Heyman, of Stockholm, stated that in something over 800 cases of adenocarcinoma treated in the Radiumhemmet, fifty-five were considered doubtful by the pathologists, but were treated as cancer. Would it not be a real gain to cut down this large doubtful group by a little more intensive study than these doubtful cases have thus far received?

THE USE OF MULTIPLE SOURCES OF RADIUM WITHIN THE UTERUS IN THE TREATMENT OF ENDOMETRIAL CANCER*

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PROGNOSIS in cancer depends largely upon the stage of clinical advance. The degree of involvement cannot be estimated accurately, however, by either duration of symptoms or size of the primary lesion. Wide variations in clinical behavior occur in different individuals despite origin of cancer in the same type of tissue or organ. The onset of symptoms may be delayed until considerable advance in tumor growth has occurred. Other patients present operable lesions in spite of clinical symptoms present for relatively long periods. Small tumors may undergo prompt dispersion to regional and distance lymph nodes. With delay in spread, large bulky cancers of doubtful localization may be completely within an operable stage.

Differences in clinical behavior are due to variations in biologic properties of tumor growth. The effect of those properties on end results may be more complex, however, than is indicated on the basis of dispersion alone. Their effect upon prognosis may be greater among patients treated by irradiation. Interactions between cancer cells and normal tissues of the host result in variation in life span for different tumors of comparable clinical extent. Those values are reflected in clinical statistics, and until there is greater knowledge of biologic factors of tumor growth, it will be difficult to evaluate different methods of treatment on the basis of survival rates alone.

Among biologic factors believed to affect prognosis in endometrial cancer is the relationship between histologic type and end results. Better survival rates are shown for well differentiated tumors. One might expect undifferentiated forms to be more sensitive to radiation. It should be noted, however, that favorable radiosensitivity is not synonymous with curability.

Healy and Cutler¹ found radiation more apt to destroy differentiated types. Healy and Brown,² Bowing and Fricke,³ and others believe histologic typing to be of less prognostic significance for treatment by radiation alone. Miller⁴ was unable to find in histologic appearance a basis for selecting a suitable method of treatment. There is, therefore, variation in interpretation of the importance of histopathology in estimating prognosis, but the relationship to survival rates is well established.

Size of the uterus is also believed to affect prognosis. Healy and Brown² found better results among patients with uteri of normal dimensions. Uterine

*Presented, by invitation, at the Seventieth Annual Meeting of the American Gynecological Society, the Seignior Club, Montebello, Quebec, June 17 to 19, 1947.

size forms the basis for clinical classifications used by Miller and Henderson,⁵ Crossen⁶ and others. With enlargement there is apt to be distortion of the intrauterine cavity. Many years ago Sampson⁷ noted the technical problems involved in radium treatment of such lesions.

Cancer of the corpus tends to remain within limits of the myometrium for long periods after onset of the tumor. For that reason a high percentage of patients are "clinically" or "technically operable" at the time diagnosis is established. In spite of considerable variation in survival rates reported for surgery alone, several authors^{5, 8, 9, 10} have shown on the basis of collected statistics that the average result from hysterectomy is on the order of 60 per cent. That value indicates that about 40 per cent of all "clinically operable" patients have extensions outside the volume of tissue removed surgically. It is interesting to note that operable stages of cervical cancer show about the same incidence of lymph node involvement. Corsecaden⁸ states that many recurrences in cancer of the body of the uterus are at or adjacent to the vaginal wound and in the abdominal scar. The intimate relationship between uterine and vaginal lymphatics may be a factor in local reappearance, as vaginal metastases are not uncommon for endometrial lesions. Additional data on lymphatic dispersion may also reveal that corporeal cancer is disseminated more often than cervical carcinoma through ovarian lymphatics with connections to the more distant and secondary barrier of nodes along the aortic chain. In the attempt to lessen treatment failure due to dispersion as well as to contamination of the abdominal wound at laparotomy, a great many authors have advocated the use of preoperative irradiation. Miller and Henderson⁵ have preferred the use of x-rays. Others have employed only radium, and some have used both methods in conjunction with hysterectomy. All have reported some improvement in clinical results, but the degree of advance is variable for different series. Corsecaden⁸ believes that average results for the combined treatment may approach five-year survival rates on the order of 80 per cent. Scheffey, Thudium, Farrell, and Hahn¹¹ emphasize the importance of a planned technique, and the reporting of results on the basis of treatment employed.

The use of preoperative irradiation has resulted in another index for evaluating the end result to be expected. Among 119 hysterectomies done after the application of about 3,600 mg./hr. of radium, Taylor and Becker⁹ reported persistence of tumor in 49.6 per cent. In that group the absolute five-year survival rate was 44.1 per cent. Among those in whom no tumor was identified the value was 73.8 per cent. Destruction of cancer within the uterus is obviously an accurate indicator of the biologic response attained by irradiation. In responses of that order it is reasonable to believe that favorable changes were obtained in tumor cells located at more distant points.

Stowe¹² has pointed out that thoroughness of search for residual cancer is not often specified and that many authors have failed to correlate observations with the amount of radiation applied. By careful review of gross specimens previously examined by routine laboratory study, persistent tumor was found in a few specimens reported as negative. The increase was on the order of 10 per cent. Tumor destruction occurs more frequently among well-differentiated types in uteri of small size. Persistence is often found at points of invasion into the uterine wall. Rarely have more than 50 per cent of specimens in a given series been free of tumor at the time of hysterectomy. Special apparatus, such as hysterostats, etc., have been devised in the attempt to treat more adequately patients with endometrial cancer. By use of those techniques a greater incidence of tumor destruction is to be expected. Variations noted for radium treatment have been due in part to the adverse effect of uterine enlargement and distortion of the cavity.

Heyman and Benner¹³ have developed one of the most efficient methods for applying radium within the uterus. Multiple tubes containing small quantities of radium are placed individually into the uterine cavity until all available space is filled. The contribution in dose from each source is small. By that means the risk of focal necrosis is lessened. In cavities of larger size the number of tubes employed is greater, thereby increasing the total amount of radium. The distribution of sources is essentially independent of distortion in shape or increase in space within the uterine cavity. From 1914 to 1933 a total of 354 patients were irradiated by means of a single linear source containing between 35 and 45 mg. radium. For that group the five-year survival rate was 45 per cent. Between 1934 and 1939 a total of 316 patients were irradiated by packing the uterus with weaker tubes of equal size and shape in sufficient number to fill the uterine cavity. For that group the five-year survival rate was 65 per cent. Heyman obtained by that method in all patients with corpus cancer a result equal to the average survival shown in collected statistics for hysterectomy alone in operable patients.

In the attempt to simulate the technique devised by Heyman, the method of radium treatment used at the Barnes Hospital and the Barnard Free Skin and Cancer Hospital was modified in 1938. Prior to that time intrauterine treatment had been given by means of tandems containing from two to three tubes in linear arrangement. That applicator did not always meet the standard requirement of active length extending from the level of the external os to the top of the fundus. The first modification consisted in the use of small strips of gauze to hold in position multiple tubes of radium packed into the uterine cavity.¹⁴ The gauze was also intended to provide some distance between the stronger sources and immediately adjacent tissues. The method was not satisfactory. Many technical difficulties were eliminated by a special instrument developed in 1940.¹⁵ By means of an introducer the number of tubes placed within the uterus was increased considerably. Brass capsules of a standard external diameter were obtained for radium sources available at the institutions in question. Length of capsules varied according to length of the radium tubes, but in each instance the strength per centimeter active length was on the order of 5 or 6 mg. of radium. From ten to twelve such capsules can be packed into a uterine cavity of normal size. Capsules of greater external diameter are used in the cervical canal to maintain patency adequate for removal of the intrauterine radium. Stronger sources are used in the cervical capsules because there are no closely related tubes contributing materially to the dose falling at that region. More recently the use of intravaginal radium has been added to the procedure. Applicators are cut from sponge rubber to fit the vaginal vault. Radium sources are then buried in the rubber at suitable points. Patients receive a course of external irradiation with x-rays before the application of radium. Four pelvic fields are selected for treatment and approximately 400 roentgens (air) applied each day. Total doses to each area are on the order of 1,200 to 1,600 roentgens. Other physical factors are: 200 KV., 0.5 mm. cu. filter, 50 cm. target-skin distance, and skin fields measuring 10 cm. by 15 centimeters. The beams are angled medially a few degrees for directing the radiation toward the center of the pelvis.

Between 1936 and 1941, inclusive, a total of ninety-three patients with endometrial cancer were treated on the ward and teaching services of the two institutions. In the earlier years of that period radium treatment was given by means of intrauterine tandems. During that period there was transition to the use of multiple capsules and routine application of x-rays and radium before hysterectomy. A few selected patients were treated by surgery alone.

The five-year end results are given in Table I. Patients treated by radiation alone were considered inoperable due to advanced cancer, or to constitutional disorders that increased the risk of surgery. That group represents approximately 45 per cent of the entire series with an absolute five-year survival rate of 27 per cent. There has been no division into "technically operable" and "inoperable" groups because the number of patients is small. Surgery was employed in 55 per cent of the series. Among those treated preoperatively with x-rays and radium there is a survival rate of 68 per cent. Hysterectomy was the only treatment procedure in 18 patients, of whom 84 per cent were alive and well at the end of five years. The absolute result for the entire series of 93 patients is 53 per cent.

TABLE I. CLINICAL RESULTS IN 93 PATIENTS WITH CORPUS CANCER TREATED FROM 1936 TO 1941 (THE HIGH SURVIVAL RATE FOR HYSTERECTOMY ALONE IS PROBABLY DUE TO THE SELECTION OF FAVORABLE CLINICAL MATERIAL)

TREATMENT	NUMBER OF PATIENTS	LOST OR DEAD	LIVING AND WELL	
			NUMBER	PER CENT
Radiation alone	43	31	12	27
Radiation and hysterectomy	32	10	22	68
Hysterectomy alone	18	3	15	84
Total	93	44	49	53

Explanation should be made of the high survival rate shown for hysterectomy alone. As noted earlier, the average result for surgery as established on the basis of collected statistics is on the order of 60 per cent. The high value shown here can be attributed to selection of favorable clinical material during the transition to routine preoperative irradiation. Among the eighteen patients treated by hysterectomy alone, well-differentiated tumors were found in fourteen. The uterine cavity measured less than 4 inches in depth in fifteen of the specimens. In one patient the diagnosis of cancer was established only after microscopic examination of the uterus removed for myoma. In two patients the cancer was apparently removed by curettement, as no evidence of tumor was identified in the specimens obtained at hysterectomy. The tumor was found to be localized and measured less than 2.0 cm. in diameter in five instances. Tumors of 2.0 to 4.0 cm. diameter were found in five specimens. No measurements are noted in the records of the remaining patients, but it is obvious that the majority of the lesions were quite early and presented favorable prognoses.

More important data can be obtained by comparing the effectiveness of radium treatment by tandem with results from irradiation by multiple capsules. In Table II is shown correlation of histologic type of tumor with method of

radium treatment in relation to five-year results. Patients treated by irradiation alone are considered separately from those in whom radiation was combined with hysterectomy. Histologic classification has been made on the basis of four different types described by Healy and Cutler.¹ These have been divided numerically into adult and undifferentiated forms. A summary of results is given for each of those divisions in the group treated by radiation alone, and for those who received the combined treatment. Better results were obtained in the well-differentiated tumors in both instances. For radiation alone, the five-year survival in adult types is 30 per cent, and 25 per cent in undifferentiated forms. For radiation combined with hysterectomy the values are 74 per cent and 55 per cent, respectively.

TABLE II. CORRELATION OF HISTOLOGIC TYPES OF TUMOR WITH METHOD OF RADIUM TREATMENT AND FIVE-YEAR END RESULTS

HISTOLOGIC TYPE	METHOD OF RADIUM TREATMENT	NUMBER OF PATIENTS	LOST OR DEAD	LIVING AND WELL	
				NUMBER	PER CENT
Radiation Alone					
I-II	Tandem	12	9	3	25
	Multiple capsules	11	7	4	36
	Summary	23	16	7	30
III-IV	Tandem	6	5	1	16
	Multiple capsules	14	10	4	28
	Summary	20	15	5	25
Radiation and Hysterectomy					
I-II	Tandem	7	2	5	71
	Multiple capsules	16	4	12	75
	Summary	23	6	17	74
III-IV	Tandem	6	4	2	33
	Multiple capsules	3	0	3	100
	Summary	9	4	5	55

The effect of histologic type on end results is more variable in a comparison of tandem treatment with multiple capsules of radium. Among patients treated by irradiation alone, the well-differentiated lesions show for tandems and multiple capsules values of 25 per cent and 36 per cent, respectively. For the undifferentiated tumors the use of tandems resulted in a 16 per cent survival, but 28 per cent of those treated with multiple capsules were alive and well at the end of the five-year period. Among patients in whom radiation was used in conjunction with surgery the end results in adult types of tumor are essentially equal for radium treatment by tandem and by multiple capsules. In the undifferentiated tumors there is wide discrepancy in results for different methods of radium treatment, but the number of patients is small.

Table III shows correlation of uterine size with method of radium treatment and five-year statistics. A depth of four inches as measured by sounding the uterine cavity has been chosen arbitrarily as a method for distinguishing the smaller and larger uteri. Among patients treated by radiation alone a survival rate of 30 per cent is shown for the group with uteri measuring less than four inches in depth. The value for patients presenting uterine enlargement is 22 per cent. For treatment by irradiation used in conjunction with surgery the survival rates are 70 per cent and 66 per cent respectively.

TABLE III. CORRELATION OF SIZE OF UTERUS WITH METHOD OF RADIUM TREATMENT AND FIVE-YEAR END RESULTS

DEPTH OF UTERUS (INCHES)	METHOD OF RADIUM TREATMENT	NUMBER OF PATIENTS	LOST OR DEAD	LIVING AND WELL	
				NUMBER	PER CENT
Radiation Alone					
Less than 4	Tandem	14	10	4	29
	Multiple capsules	20	14	6	30
	Summary	34	24	10	30
More than 4	Tandem	4	4	0	0
	Multiple capsules	5	3	2	40
	Summary	9	7	2	22
Radiation and Hysterectomy					
Less than 4	Tandem	11	5	6	55
	Multiple capsules	15	3	12	80
	Summary	26	8	18	70
More than 4	Tandem	2	1	1	50
	Multiple capsules	4	1	3	75
	Summary	6	2	4	66

Upon considering the effect of method of radium treatment it is interesting to note that in patients treated by irradiation alone the use of radium tandems resulted in a 29 per cent survival in smaller uteri, but none of the four with uterine enlargement survived five years. For multiple capsules of radium the value for smaller uteri is 30 per cent, which is practically identical to that obtained for tandems, but two patients survived in the group of five with uterine enlargement. The superiority in results for multiple capsules in larger uteri is due to improvement in distribution of radiation and increase in tissue dose. In small uteri the advantage of multiple capsule treatment is less evident, because tandems may fill space within the uterus with reasonable completeness.

Analysis of results from radiation combined with hysterectomy involves consideration of only a few patients with uterine enlargement. In the smaller uteri the result from preoperative tandem of radium is 55 per cent. For multiple capsules the value is 80 per cent. Among those with uterine enlargement, one (50 per cent) of the two treated by tandem is alive at the end of five years, but 75 per cent survived after irradiation by multiple capsules.

Variation in survival rate is to be expected for both histologic type and uterine size. The attempt to compare different technique of radium treatment in correlation with only one of those factors is made complex by the effect of the other. In the small series presented here, data upon improvement in clinical results for the use of multiple capsules of radium are more conclusive if comparison is made on the basis of method of radium treatment only. In Table IV it can be seen that the use of tandems in patients treated by irradiation alone resulted in a survival rate of 22 per cent. For multiple capsules of radium the result is 32 per cent. Patients treated by irradiation and surgery show for tandems a value of 54 per cent. A total of nineteen patients received multiple capsules of radium before hysterectomy. Of that group fifteen, or 79 per cent survived the five-year period. Mention should be made of the 18 patients treated by surgery alone shown in Table I. Of that group fifteen, or 84 per cent

were alive and were at the end of the same period. The two groups are essentially equal in number and in end results. The fact that the patients receiving preoperative irradiation were not from selected clinical material indicates, however, that the average prognosis was less favorable.

TABLE IV. CORRELATION OF METHOD OF RADIUM TREATMENT WITH ABSOLUTE FIVE-YEAR RESULTS

METHOD OF RADIUM TREATMENT	NUMBER OF PATIENTS	LOST OR DEAD	LIVING AND WELL	
			NUMBER	PER CENT
<i>Radiation Alone</i>				
Tandem	18	14	4	22
Multiple capsules	25	17	8	32
<i>Radiation and Hysterectomy</i>				
Tandem	13	6	7	54
Multiple capsules	19	4	15	79

The effect of histologic type on end results may be largely a factor of tumor dispersion. The effect of uterine size may be due to tumor bulk and dispersion, but includes also technical problems involved in attempting to obtain a suitable distribution of radiation. Of importance in response to radiation are biologic properties affecting radiosensitivity. Disappearance of cancer as determined by examination of tissue removed at hysterectomy performed after preoperative treatment presents a more accurate estimate of tumor response. Patients presenting specimens free of cancer should have an excellent prognosis.

Data on microscopic findings in uteri removed after irradiation are given in Table V. The persistence or absence of recognizable tumor has been made on the basis of routine laboratory examination. Careful review of all specimens might reveal viable cancer in some reported previously as negative. Errors in identification should be equal for treatment by tandem and by multiple capsules. The data are suited to comparing the two methods of radium treatment in question.

Included in the table are results reported by Taylor and Becker⁹ for 119 hysterectomies done after the application of approximately 3,600 mg./hr. radiation by intrauterine tandem. The total results for the series presented here are in remarkably close agreement with those published by the authors mentioned above. Taylor and Becker found persistent tumor in 49.6 per cent of their patients. In that group the five-year survival was 44.1 per cent. For the thirty-two patients in the series reported here, persistent tumor was found in 47 per cent with five-year survival of 46 per cent. Taylor and Becker were unable to find viable tumor in 50.4 per cent of their patients who showed a survival rate of 73.8 per cent. In our series 53 per cent were without recognizable tumor, and of that number 88 per cent survived the five-year period. The destruction of tumor in the uterus is obviously an important and favorable prognostic sign. Further analysis of the series here reported shows poor results for treatment by intra-uterine tandem as compared with those published by Taylor and Becker. Improvement is shown, however, for the use of multiple capsules. Among the thirteen patients treated by radium tandem, persistent tumor was

found in ten, or 77 per cent. Of the nineteen in whom multiple capsules of radium were employed, only five, or 26 per cent, had recognizable cancer. A technique of radium treatment that will destroy cancer within the uterus in three-fourths of patients treated by that method should advance materially the clinical results obtained in cancer of the uterine corpus.

TABLE V. CORRELATION OF PERSISTENCE OF TUMOR WITH METHOD OF RADIUM TREATMENT AND FIVE-YEAR END RESULTS*

METHOD OF RADIUM TREATMENT BEFORE HYSTERECTOMY	TOTAL NUMBER OF PATIENTS	PERSISTENT TUMOR			UNIDENTIFIED TUMOR		
		NUMBER OF PATIENTS	PER CENT OF TOTAL	PER CENT SURVIVAL	NUMBER OF PATIENTS	PER CENT OF TOTAL	PER CENT SURVIVAL
Tandem	13	10	77	40	3	23	100
Multiple capsules	19	5	26	60	14	74	85
Total	32	15	47	46	17	53	88
Taylor and Becker ^a	119	59	49.6	44.1	60	50.4	73.8

*Comparison is made with the larger series reported by Taylor and Becker.

Relationship can be established between tumor disappearance and histologic type. Of the thirty-two patients treated by hysterectomy after irradiation, twenty-three had well-differentiated tumors with persistent cancer found in only six, or 26 per cent. There were nine patients with undifferentiated tumors, of whom seven, or 77 per cent, showed recognizable cancer. Others have observed the greater incidence of destruction for tumors of higher differentiation. The tendency for undifferentiated forms to survive may be due in part to invasion of the uterine wall with increase in distance between some cancer cells and different sources of radium, and to greater ability for recovery of cells not destroyed completely by irradiation.

The destruction of tumor is also associated with size of the uterus. That is particularly true for treatment by radium tandem. The multiple capsule method is, however, essentially independent of uterine size. Evidence that cancer within the uterus can be destroyed in about three-fourths of the patients is shown in experience with the multiple capsule technic since the years included in this report. From 1942 to 1946 a total of thirteen patients received multiple capsules of radium prior to hysterectomy (the study was partially interrupted during the war years). The addition of those patients to the nineteen here reported presents a total of thirty-two treated by the method in question. For that number 71 per cent were without identifiable tumor.

The amount of radiation applied by radium is, of course, important in determining immediate and end results. Of the thirteen patients upon whom hysterectomy was performed more than five years ago after treatment by radium tandem, there were six who received between 3,000 and 4,000 mg./hr. radiation. Between 4,000 and 5,000 mg./hr. were applied to six of the remaining number, and one received an amount slightly in excess of 5,000 mg./hr. radiation. For that method the dose per source was on the order of 1,200 to 1,600 mg./hr. radiation. Such amounts are to be expected to produce tissue necrosis, and areas of severe damage were noted frequently.

Among the nineteen patients treated by multiple capsules before hysterectomy, there were eight who received between 3,500 and 5,000 mg./hr., and eleven in whom the total dose ranged between 5,000 and 7,000 mg./hr. radiation. The larger amounts were delivered by the more recently used technique employing an introducer for weak sources of approximately 6.0 mg. radium strength per centimeter length. In those instances the average dose per source is on the order of 450 to 600 mg./hr. radiation. An intense reaction is produced throughout the uterus, but areas of severe damage with necrosis are found rarely. The histologic changes were described in an earlier publication.¹⁵

Severe damage by radiation can produce untoward sequela. Necrosis of normal tissues in the tumor bed can result in unrestrained growth of cancer rather than control of the lesion. In clinical practice maximum and minimum tissue doses become important. In the case of radium, points near the different tubes receive the greater amount. The fall in intensity of dose is enormous within the distance of only a few millimeters. Cancer cells located at short distances from radium tubes will receive a minimum tumor dose that may be inadequate for their destruction. Improvement in distribution of radiation acts to lessen discrepancy between minimum and maximum tissue doses. For any increase in number of radium tubes contributing to the total dose there will be improvement in distribution of radiation. Due to contribution from several sources, the dose per unit becomes less important and, consequently, can be made less than would be required for the same total dose delivered by a lesser number of irradiating sources. By that means it may be possible to treat adequately a greater volume of tissue by increasing the minimum dose delivered to more distant points, without undue risk of overtreatment near radium tubes. The use of multiple capsules meets that requirement and accomplishes an improvement in results by the administration of greater amounts of radiation.¹⁶

For the method in question there is risk of uterine perforation. Such an accident has been recognized in only two instances. One has been reported previously, and occurred with the technique employing the introducer and special capsules.¹⁵ The other occurred with the use of tubes of various size and strength in which gauze was employed. In the latter instance a radium tube had become lost in the abdomen and necessitated laparotomy for removal. Neither patient with perforation survived the five-year period free of recurrence.

Hysterectomy has been performed at different intervals after radium treatment. In some patients with a lapse of only one week there has been disappearance of tumor indicating that the effect of radiation is more prompt than generally appreciated. With intervals of six weeks there has been evidence indicating recovery and renewed growth of tumor not destroyed completely. Upon that basis it appears that hysterectomy should be done as promptly as possible. The average interval has been about four weeks, but in all instances the determining factor rests upon the condition of the patient. For the most part there will be sufficient recovery from local and constitutional effects of radia-

tion by that time to permit safe performance of surgery. The use of large amounts of radiation before operation results in technical problems for hysterectomy, but those have not been of a serious order, and seem justifiable upon the basis of improvement in clinical results.

Summary and Conclusions

About 1938 a planned method of treatment was established for patients with corpus cancer at the Barnes Hospital and the Barnard Free Skin and Cancer Hospital. The method of radium treatment was changed from one employing intrauterine tandems to a technic using multiple capsules of radium packed individually into the uterine cavity in the attempt to fill all the available space. The use of radium is preceded by the external application of x-rays. Patients suited to hysterectomy are given preoperative irradiation with both x-rays and radium.

Between 1936 and 1941, inclusive, a total of ninety-three patients with corpus cancer were treated on the ward and teaching service of the two institutions. The period of years included in the report antedates the onset of a planned method of treatment. In the earlier years radium was applied by intrauterine tandem. During the transition to regular use of preoperative irradiation, a few selected patients with favorable prognoses were treated by hysterectomy alone. Of the entire group of ninety-three patients, 45 per cent were considered inoperable due to advanced cancer, or to some constitutional disorder. The absolute five-year survival rate for the forty-three patients treated by irradiation alone is 27 per cent. For the thirty-two patients receiving preoperative x-rays and radium followed by hysterectomy the five-year result is 68 per cent. Surgery alone was used in eighteen individuals, of whom 84 per cent are alive and well for the same period. Explanation of the unusually good results from hysterectomy alone is made on the basis of favorable clinical material. The absolute five-year survival for the entire series of ninety-three patients is 53 per cent.

The attempt is made to compare the relative effectiveness of treatment by intrauterine tandem of radium, and by the use of multiple capsules. For that comparison the effect of certain biologic properties of tumor growth are also considered in their relation to end results.

Variation in survival rate is found with histologic type for treatment by radiation alone as well as in conjunction with hysterectomy. Better results were obtained in the more highly differentiated forms. An improvement in clinical results is shown for the use of multiple capsules.

Variation in survival rate is found also with size of the uterus. For treatment by radiation alone the results in uteri of small size were about equal for tandems and multiple capsules. In those instances a linear arrangement of radium tubes may fill the uterine cavity with reasonable completeness. Among the four patients with large uteri, however, there are no survivors for treatment by x-ray and radium tandem alone. The use of intra-uterine tandems in conjunction with surgery resulted in survival of about half of the patients. Only two showed enlargement of the uterus. The results from multiple capsules and

hysterectomy appear essentially independent of uterine size. About three-fourths of each group survived the five-year period.

Despite the fact that survival rates are affected by both histologic type and uterine size, and improvement in clinical results can be shown for the use of multiple capsules by comparison made on the basis of method of radium treatment only. Among patients treated by radiation alone the use of intrauterine tandems resulted in survival of only 22 per cent, but 32 per cent of those irradiated with multiple capsules are alive and well at the end of the five-year period. For treatment by irradiation and hysterectomy the use of intrauterine tandems resulted in survival of 54 per cent, but the value for multiple capsules of radium is 79 per cent.

More reliable than histologic type or uterine size in establishing the clinical result to be expected is the persistence or disappearance of tumor within the uterus after preoperative irradiation. Among the thirty-two patients treated by hysterectomy after the use of x-rays and radium, persistent tumor was identified in 47 per cent. Of that group only 46 per cent survived the five-year period. Among the patients in whom no tumor was identified the survival rate is 88 per cent. Persistent tumor was found in 77 per cent of the patients irradiated by tandems. Only 26 per cent of those in whom multiple capsules were employed showed viable cancer in the specimen removed at hysterectomy.

In view of the 88 per cent survival for patients without recognizable tumor within the uterus, it should be noted again that no residual cancer was recognized in three-fourths of specimens previously irradiated by multiple capsules of radium. Furthermore, fifteen (79 per cent) of the nineteen patients treated by multiple capsules and hysterectomy are alive and well after five-years of observation. Those patients were not selected clinical material as were the eighteen treated by hysterectomy alone. Having attained essentially equal results in both groups seems to establish for the small series an improvement in clinical results for preoperative irradiation by multiple capsules of radium.

Discussion is given upon the improvement in distribution of radiation and in tissue dose for multiple sources of radium within the uterus. By means of that method it has been practical to increase the total amounts of radiation employed. Accidental sequelae in two patients are described, and the interval of time between preoperative irradiation and hysterectomy is discussed.

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Discussion

DR. FRANKLIN L. PAYNE, Philadelphia, Pa.—The crux of this presentation lies in the question: is the multiple small source intrauterine distribution of radium worth the trouble and the risk that it entails? General dissatisfaction with the older methods of application has stimulated the introduction of many devices that aim at more accurate radium placement. In the effort to accomplish this objective we use a modification of the Crossen wire technique with moderate success, as evidenced by x-ray study. A total of 5,000 to 6,000 milligram hours of radium is administered in one or two sittings by distributing seven to ten capsules of 10 milligrams each in the uterine cavity. By a simple maneuver we place one or two capsules across the top of the cavity at right angles to the cervical canal. This technique has not been in use sufficiently long for us to judge the results in terms of survival rates. We can say, however, that we are impressed with the more uniformly disseminated effect of the irradiation as we study the removed uteri.

Dr. Arneson states that his plan is a modification of the Heyman packing method. He is to be congratulated upon the first report in this country concerning the clinical results of this procedure. While his samples are not large enough to serve as conclusive statistical evidence, they do suggest that his plan offers great promise. Undoubtedly, it is far more troublesome than the older method. Furthermore it is slightly more dangerous, as indicated by two perforated uteri in the present series and three similar accidents that Heyman reported to have occurred during a thousand applications. When the obvious theoretic advantages of the procedure are supported by highly suggestive evidence of its clinical superiority, the bother and the slight additional risk seem to be compensated fully. (*The British Journal of Radiology*, March, 1947) Heyman advanced his five-year survival rate from 45 per cent in 354 patients to 64.9 per cent in 316 patients by means of his packing method. By condensing Arneson's charts we see that following the use of multiple capsules his salvage rate rose from 35 per cent to 52 per cent. The apparent explanation for this improvement is seen in Tables III and V, based upon seventy-five patients who were treated by either irradiation alone or by irradiation and surgery. In Table III, forty-three patients received only irradiation and the survival figures were 10 per cent better following multiple capsules than they were after the tandem application. Of thirty-two patients who were treated by surgery after irradiation the packing technique was followed by a 25 per cent better survival rate. In Table V, which depicts persistence of the tumor after irradiation, Arneson found the growth to remain three times as frequently after tandem sources than it did after multiple sources. In the same table his figures indicate that the chance of survival is almost twice as great if the tumor is destroyed by irradiation prior to operation.

Consideration of these interesting figures, although they are based upon small groups of patients, does suggest that some form of intrauterine multiple small source radium distribution is a worth-while procedure.

DR. LEWIS C. SCHEFFEY, Philadelphia, Pa.—Dr. Arneson and his associates have presented convincing evidence of the fact that preoperative irradiation with radium offers better end results in the treatment of fundal carcinoma than does primary surgery alone. This is in line with a belief that we have entertained personally for many years, a belief that has been shared by others working in this particular field.

This study leads into several interesting by-ways of investigation with respect to the importance of tumor gradation, size of the uterus, persistence of tumor after irradiation, and irradiation in relation to prognosis. Certain valid correlations, or at least a trend toward such correlations, seem to have been established.

Of most importance, and certainly as regards the life of the patient, is the relatively higher survival rate attained by Dr. Arneson through the use of the multiple capsule technic

in preference to the older tandem technic. However, one must bear in mind that perhaps two factors may perhaps influence these improved statistics.

First, it is likely that the more recent use of the multiple capsule method when compared with the tandem method, would naturally present a higher survival rate among those patients more recently treated, when compared with the patients treated earlier, and who are now in the older age group. Second, the additional use of external irradiation before the preoperative radium application.

Nevertheless, when another factor is taken into consideration, namely, persistence of tumor in the removed uterus, it certainly seems that multiple sources of radium are distinctly advantageous in destroying the malignancy and retarding recurrence.

I would like to know what the incidence of concomitant fibromyomas was in the series presented. Their presence often accounts for the uterine enlargement to the exclusion of the cancer itself, especially with respect to the distortion of the uterine cavity.

In relation our own experience with this problem (Jefferson Hospital), I shall confine myself to but one phase, viz., results with the tandem technique where a planned procedure for the treatment of fundal cancer was possible. The broader problems associated with the management and treatment of fundal carcinoma in general have been taken up in the recently published article of ours that Dr. Arneson referred to. It has been our feeling at Jefferson Medical College Hospital that the tandem technique of intrauterine radium possesses distinct advantages apart from the actual treatment of fundal cancer itself, and especially in one respect. The possibility of endometrial malignancy must naturally be considered abnormal uterine bleeding at the menopause. Visual and palpatory examination offers nothing conclusive. In the management of such patients, radium therapy is often ideal. Accordingly, we always have radium capsules (25 or 50 mg.) available when the diagnostic curettage is to be carried out. An excellently prepared histologic section of the curettings is then available in four hours or less. An intracavitary application of radium is made immediately following the curettage, and in tandem if the character of the uterine cavity permits. Should the report prove benign a suitable dosage is decided upon, following which the capsule or capsules are readily removed; if malignant, dosage adequate for cancer can be employed, and adequate surgery follows in about six weeks if the patient is a suitable risk. Such a procedure, it seems to me, would not be so easily carried out with the multiple units described by Dr. Arneson.

Employing the plan mentioned, I may state that during approximately fifteen years we have treated in this fashion seventeen patients with fundal carcinoma eligible for five-year statistics. Fifteen are living from five to fifteen years later, indicating a survival rate of 89.2 per cent. In approximately 50 per cent, residual malignancy was present. External irradiation has played no part whatsoever in the treatment of these selected patients, and there was no primary mortality.

During the past four years or more, but not eligible for five-year evaluation, we have treated thirty-nine additional patients with fundal carcinoma in this way, with thirty-seven survivors to date, also without primary mortality.

On the basis of this accomplishment, I am loath to change our present plan of therapy for fundal cancer, but I am frank to confess that Dr. Arneson's valuable presentation may change our viewpoint to some extent, especially with respect to those patients in our consecutive series who are not suitable for subsequent surgery for one reason or another.

DR. DANIEL G. MORTON, San Francisco, Calif.—With regard to the effort to develop a method whereby radioactive substances may be applied to the inner surfaces of the uterus in endometrial cancer in a more efficient manner than is afforded by a simple tandem of two, three, or four pieces of radium, I should like to report briefly an experiment which we carried out at the University of California in 1943 and 1944. At that time, due to the development of the cyclotron, certain radioactive solutions, namely radioactive phosphorous and radioactive strontium, became available. It occurred to us that we might possibly use these solutions to effect an even distribution of radiation within the uterine cavity. A solution should have the property of filling out all of the crevices and interstices of a growth in a manner which

could not possibly be duplicated in any other way. The main problem, of course, would be to distend the cavity fully and yet retain the solution within the uterus without leakage through the tubes or from the cervix. In order to do this we used the water-containing unit of the Foley catheter—not entirely satisfactory, but approximating what we sought; i.e., a very thin rubber sac which could be distended under pressure after introduction. Presumably, whatever the shape of the cavity, it would be filled out. Anywhere from 4 to 13 c.c. were used in the four cases in which this method was used. The material was left in place for forty-eight to seventy-two hours. We had an opportunity to examine the uteri later in all cases, because subsequent hysterectomy was performed in three cases, and an autopsy was performed in the fourth case, when the patient died only a few weeks later.

In all cases it was found that there was superficial necrosis of the growth, or of the fibromuscular tissue of the uterine wall, in areas where no tumor existed and the endometrium was thin. The maximum depth of the reaction was about 2 mm. At greater distances from the surface "healthy" cancer cells remained. So our experiment was a failure, but we believe that the idea is a good one and susceptible of development. The solutions we used give off B rays only—not gamma rays. We believe that the failure to penetrate deeper is related to this fact.

It now appears that other radioactive solutions will become available; e.g., radioactive cobalt, from which gamma rays emanate. We plan to try some such solutions. The matter of dose and mode of application will of course require considerable thought. However, the general idea we believe to be worthy of further research.

DR. CURTIS F. BURNAM, Baltimore, Md.—We have been using multiple sources of radiation in Baltimore for many years: in fact, my first paper published in the early 20's on the treatment of adenocarcinoma of the uterine body was on cases treated in this way. In Curtis' *Gynecology* the method is shown. There can be no doubt that in uterine body carcinoma irradiation more effective treatment is obtained by multiple sources than by tandem arrangement.

We feel, too, that in body carcinoma it is very important to irradiate the cervix and the vagina. It is extraordinary how often a metastasis occurs in the vagina from cancer of the body of the uterus.

The dosage that we have employed has varied with the size of the uterus and the character of the cavity. We never use ordinary tandems; our sources are not radium but radon, and we use bulbs 2 to 3 mm. in diameter. The dosage in a small uterus is hardly ever over 2 gramme hours. In large uteri where there are fibroids for example, we give twice that much or more. It is important to take the individual unit and to calculate the dosage in the volume around it.

I have not had much success in treating body cancer with x-ray. After adequate intra-uterine radiation, an additional amount of x-ray has greatly increased small bowel and sigmoid injuries, i.e., an amount of x-ray that could be beneficial.

We usually use in radon the equivalent of 2 Gm. of radium. The treatment in a small uterus can be given in one hour. Also, there are many cases of body carcinoma which have complications. What would you do, Dr. Arneson, in a case of pyometrium? We have tried to clear up the infection and then use intrauterine radium. I am convinced that the best method of treatment in cancer of the uterine body is the combination of radiation and operation.

DR. NORMAN F. MILLER, Ann Arbor, Mich.—I appreciate the fact that Dr. Arneson is talking specifically about intracavitary radiation. I am moved, however, to say just a word about another form of radiation, namely deep x-ray, as a supplemental means of treating corpus cancer. Our aim is to cure the greatest number of patients. Radiation by the intrauterine placement of multiple capsules is one of the better methods of achieving good results, especially when used in combination with operation later on. However, we should not be blinded to the value of high-voltage x-ray treatment in the management of this condition. We have used x-ray as a preoperative measure in the management of corpus car-

cinoma in our clinic (University of Michigan Hospital) for about fifteen years. At the last meeting of this Society I reported on approximately 100 cases so treated and pointed out that by this method we had obtained 77 per cent five-year and 65 per cent ten-year survivals.

I believe the use of x-ray gives more thorough parametrial treatment than can be accomplished by intracavitary radium.

DR. SUBODH MITRA, Calcutta, India.—I would offer some criticism of Dr. Arneson's paper in that the evidence from this material is not sufficient to draw any statistical conclusion. In one of the groups he had four cases and we do not know how many of those are dead, and how many lost sight of; so it is very difficult to express any opinion in that respect.

The next point to be decided is which is the best method of treatment for carcinoma. The application of radium by capsules is as good as an operation itself. I have seen the work of Dr. Heyman who has found very satisfactory results by using multiple capsules alone without any subsequent operation. I have also had some operative cases of my own with good results. Under the circumstances one must think seriously whether this application of multiple capsules should be supplemented by another operation. We use subsequent deep x-ray therapy only when we do the operation or give the radium treatment.

Dr. Miller offered a very valuable suggestion that x-ray does help as well as radium in treating these cases of carcinoma.

DR. ARNESON (Closing).—On a critical basis it can be said that the method of treatment in question is cumbersome, expensive, and not without risk to the patient. We have worked on the hypothesis that risk of intestinal injury is greater for x-rays than for radium. For that reason the amount of roentgen treatment has been less than is generally employed. It is sufficient, however, to produce tumor changes and to decrease the amount of infection always present. By that means the patient is better prepared for intrauterine radium, but it is not to be implied that a preliminary course of x-rays will eliminate pyometria. Any collection of pus within the uterus must be drained before radium is applied.

The effectiveness of treatment depends upon the distribution of radiation, the tissue dose obtained, and the biologic properties of the lesion. Both maximal and minimal doses falling within the tumor-bearing region are important. Maximal quantities must be less than amounts apt to produce extensive tissue damage. Minimal doses must be adequate for the control of tumor. In combinations of x-ray and radium treatment the greater amounts of radiation will fall along points near the radium tubes. If the number of irradiating sources is increased, then the contribution required from a particular tube is made less. By that means a more uniform distribution of radiation is obtained, and the minimal amount falling within the tumor can be increased. It is on that basis that Dr. Burnam has used bulbs of radium within the uterus, and that Dr. Heyman devised his technic. Dr. Morton's discussion is particularly pertinent. By the use of solutions of radioactive isotopes in flexible containers, the application can be molded into a shape corresponding to the uterine cavity. The intensity of radiation would vary only with the magnitude of projections into isolated regions.

In teaching procedures we encourage students to think in terms of the dose per source. To express treatment by the total number of milligram-hours radiation is no more correct than to attempt description of a surgical procedure on the basis of the time required for operation. We believe that the use of multiple capsules has been established as an effective clinical procedure. We hope to gain further increase in the number of radium tubes employed, with decrease in the amount of radiation contributed by each source. Mention should be made of work by Dr. Nolan. By means of special film he has studied photographically the zones of effect within phantoms for different methods of radium application. In clinical practice the use of preoperative irradiation has interfered with subsequent surgery in only a very few patients.

HIGH LYMPHADENECTOMY AND SYMPATHECTOMY IN CARCINOMA OF THE VULVA*

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THE successful treatment of carcinoma of the vulva differs in no way from that of carcinoma in other sites in that the primary lesion, the spreading growth, and the metastases in lymph nodes must be completely destroyed or eradicated.

Because the malignant vulvar tumor is situated on a part of the body which has an enormously widespread lymph drainage system, the exact limits of surgical excision required are difficult to estimate, as are the sites and dosage of radiation.

The surgeon may excise a primary tumor entirely and many near-by malignant lymph nodes, but he never knows how much of the metastatic growth is left behind. By radiation a wide area can be covered and scattered malignant tissue destroyed but recurrences indicate that the lethal rays do not strike all the cancer cells in every case.

Apart from the simplification of the many problems associated with the cure of carcinoma which earlier reporting would bring, it seems logical to conclude that more extensive surgery and heavier and wider irradiation must improve the results of treatment of carcinoma.

The reasonable limits of surgical procedure and radiation therapy are always extending side by side with discoveries and advances in many other scientific fields translated into improvements in pre- and postoperative care and operative technique. At the moment, however, it seems that the radiation therapy of vulva carcinoma and lymph node metastases, in the groin for example, is more limited than surgical excision of the affected parts and so it is that vulvectomy and lymphadenectomy are the more favored procedures.

With those premises in mind, a recent case of epithelioma of the vulva was treated by vulvectomy, inguinal, pelvic, and lumbar lymphadenectomy. Lumbar sympathectomy was also performed as a prophylactic measure against arterial spasm, venous thrombosis and excessive sweating.

The patient concerned, Mrs. H., aged 37 years, was referred to me on Feb. 19, 1947, by Dr. Baker of Campbellford, Ontario, for a nonhealing ulcer of the vulva which had been recognizable for at least one and one-half years. The carcinoma was 7.5 cm. long and occupied the right side of the vulva, stretching from the clitoris to the perineum, and from the outer edge of the labium majus to the urethra and just inside the vagina.

*Presented, by invitation, at the Seventieth Annual Meeting of the American Gynecological Society, the Seignior Club, Montebello, Quebec, June 17 to 19, 1947.

The right subinguinal lymph nodes were markedly enlarged and somewhat fixed. The left subinguinal nodes were just barely palpable. Aside from the discomfort of the vulvar growth, the patient neither felt unwell nor had she lost weight.

Vulvectomy was performed on February 21, in the course of which more tissue was removed from the right side than the left. The anterior edge of the incision on the right side passed medial to the insertion of adductor longus muscle, and was placed far enough back to allow removal of some of the fatty tissue emerging from the ischiorectal space. Both on the right side and on the left the fascia over the adductor muscles was laid bare, and within the area defined by the pubic rami the soft tissue was cleared away until the branches of the pudendal artery could be clamped as they emerged from under the edge of the bones. Medially, the incision partially ringed the urethra and then entered the vagina for about one-half inch.

In order to cover the large bare area thus exposed, the adjacent skin was undercut in all directions and, in addition, on the right side a large flap was cut from the thigh and turned medially so that its upper edge became the right side of the vaginal introitus.

Postoperative treatment followed our usual routine, which includes pressure dressing to prevent accumulation of tissue fluid, indwelling catheter for five days, prophylactic sulfadiazine for five days, penicillin up to 300,000 units, early ambulation, bed exercises, and the use of the lavatory.

The first lymphadenectomy was not performed until thirty-five days later, by which time it was hoped that any reactionary changes in the inguinal glands or those higher in the chain would have died down. The steps of the operation were based on Taussig's modified Bassett operation.¹

The left side was done on March 28. Exposure for this operation is made by an incision about seven inches long from a point one inch above and medial to the anterior superior iliac spine, and curving down to cross the middle of Poupart's ligament and continue in the line of the femoral vessels. Block dissection of the fat, nodes, and areolar tissue is begun about two inches from the termination of the saphenous vein. The vein is followed, ligated, and cut near its junction with the femoral vein. The fat and nodes are then dissected from the fascia of the anterior abdominal wall, and at the external abdominal ring the round ligament is tied and cut. The tie allows of easy identification later in the operation. The block of tissue is now dissected from all sides toward the fossa ovalis. It seems that the superficial veins and arteries are easily clamped in this way, and there is no danger of tearing the saphenous vein at its deepest point.

The femoral sheath is then opened, and any nodes lying medial to the vein are removed. The femoral canal is identified, and the gland occupying its proximal end is pulled up with an Allis forceps and removed also.

The inguinal canal is now opened, and this can be safely done by pulling on the round ligament and cutting over it with a knife. The epigastric vessels come into view on the deeper part of the round ligament and medial to it, and are tied off and cut after the conjoined tendon has been snipped with scissors. Lateral extension of this extraperitoneal opening can be obtained by cutting the fibers of the internal oblique and transversalis muscles and fascia.

With this exposure the intact peritoneal sac can be gently stripped inward from the underlying iliac vessels and lymph nodes and, although the hypogastric and common iliac nodes lie very deeply, they can be easily reached.

In this case none of the inguinal or the iliac nodes on the left side appeared to be enlarged, and it was later reported that none showed malignant tissue.

The operations of right lumbar sympathectomy and lymphadenectomy of the right lumbar, pelvic, and inguinal nodes were performed four days later.

In reviewing all the hazards of the operation in this case, hemorrhage and deep infection were regarded as possible but not probable complications, as they would be of any such procedure. A recent experience of encountering arterial spasm in the lower limb following extensive dissection of malignant nodes adherent in the region of the large vessels prompted very careful consideration of steps which could be taken to circumvent the recurrence of such an accident in similar circumstances.

In any event, hemorrhage and infection are conditions about which, perhaps, there is not the same prophylactic uncertainty as there is about such potentially serious complications as postoperative vascular spasm, thrombophlebitis, phlebotrombosis, and pulmonary embolism.

The manipulations of dissecting areolar tissue and lymph nodes surrounding the large vessels have to be performed very gently, for obvious reasons. Even with the greatest care, it is not uncommon to observe hardening, presumably spasm, of the iliac vessels, and it is known that injury of blood vessels sometimes results in prolonged vascular spasm. Oschner and DeBakey² are convinced that the clinical manifestations of inflammatory thrombosis are due to vasospasm of the arterial and venous systems beyond the lesion caused by the irritation of the venous segment affected.

Although the actual cause of venous thrombosis is not known, almost all records show that pelvic operations, especially in women, are commonly the preceding condition. There are undoubtedly many factors at work, but changes in the composition of the blood, narrowing of the vessel lumen, and stasis are etiologically very important.

As regards the possibility of producing vascular irritation and its consequences during the course of an operation, the Bassett-type of lymphadenectomy in either vulvar cancer or cervical cancer, both conditions in which infection may be present in lymph nodes and the surrounding tissues, is one which involves more handling and possible trauma of the large veins and arteries than almost any other pelvic operation in women, excepting that for cancer of the rectum. It seems logical, always assuming that there is some connection between distant thrombosis, widespread vascular spasm, and such surgical procedures to perform lumbar sympathectomy before or at the time of the pelvic operation, the primary effect of which is to produce vasomotor paralysis. It is well known, of course, that in the treatment of established thrombophlebitis, local anesthetic sympathetic block has been advocated and, also, to relieve the pain, swelling, and ulceration of chronic thrombophlebitis, lumbar sympathectomy is now widely practiced.

Shortly after sympathectomy, the extremity is dry, warm, and of good, if not a little deeper, color than before. The increased warmth is due to a marked and sustained increase in blood flow to the limb. The dryness is due to pseudomotor paralysis which completely inactivates the sweat glands.

These reactions, increased blood flow and inactivation of the sweat glands, might be considered of great advantage in vulvectomy and groin dissections for reasons not directly connected with the prophylaxis of vascular injury and vasospasm, namely, the promotion of better healing of skin flaps through in-

creased blood supply, the reduction in moisture from sweating, lessening of concomitant skin infection, and, also, avoidance of postoperative fissure at the vaginal introitus.

The extension of the range of the right lymphadenectomy to include the lumbar nodes was undertaken partly because lumbar sympathectomy was going to be done and the lumbar chain of lymph nodes would be easily accessible, and partly because these nodes form the next stage after the iliac group in the natural spread of carcinoma, even although such metastasis appears to be a late one.

In this case the retroperitoneal approach to the sympathetic chain and the lumbar glands was made through an incision starting midway between the last rib and the iliac crest and ending one inch medial to the lateral edge of the rectus muscle opposite the umbilicus. The technique of White and Smithwick³ was otherwise closely followed. The second, third, and fourth lumbar ganglia were removed with their connecting branches, and thereafter the lumbar lymph nodes were dissected out from a point at the level of the second lumbar vertebra. The upper end of the chain was cut, but the lower end was not severed, and when the packing which had been put in to keep the peritoneum and ureters displaced medially was removed, the mass of glands was tucked down toward the pelvic brim and the incision was closed.

Inguinal and pelvic lymph node dissections were then performed as described for the left side and toward the end of the operation, when the iliac nodes were freed, it was possible to pull down the lumbar chain which had already been separated.

Anesthesia for this operation consisted of spinal pontocain, 12.0 milligrams augmented during the latter half of the operation by half a gram of pentothal sodium given intravenously. The operation lasted three hours. All the glands were sectioned and squamous epithelioma was found in the inguinal and iliac glands, but malignant tissue was not discovered in the glands from the lumbar chain. Routine orders for postoperative care were carried out as usual and no complications occurred. The right leg was slightly pinker than the left and skin temperature was about one degree higher on the right than on the left.

Discussion

The three operations described constitute a heavy risk to the patient. There seems little doubt that with the unfortunately late reporting of many women with vulvar carcinoma, the pelvic lymph nodes are often involved, and because there is no means of knowing in which case this has already occurred, those lymph nodes should be excised routinely.

As Taussig has shown, there is little difference in his percentage cure rate between those who have and those who have not malignant metastases in these nodes. Watson,⁴ however, treated a series of twenty-five cases of all stages of the disease without pelvic lymphadenectomy and obtained 40 per cent five-year survival, which is 15 to 20 per cent less than that obtained by Taussig who invariably, in a selected group of cases, performed lymphadenectomy. As Watson says in his report, "If operable cases have involvement of this (pelvic) group of nodes as constantly as is indicated by some observers, the survival of any of our cases is unexplainable."

The advanced age of many women suffering from carcinoma of the vulva must of itself restrict operative procedures to a minimum, but, on the other hand, it is not the young but the aged who already may have an impaired vascular system who are more likely to develop the vascular complications of surgical operations.

Descriptive details of postoperative complications and postmortem reports on those who have died as a result of surgical treatment of this disease are exceedingly scanty in the literature, and therefore information on the relative frequency of hemorrhage, infection, thrombosis, fatal embolism, surgical accidents, etc., is not available in our small clinic (Kingston General Hospital) on which some justification for sympathectomy as a prophylactic measure can be based. If, however, the surgery of genital carcinoma is to become as radical as it is rapidly becoming in many other branches of surgery of carcinoma, then gynecologists may have to take cognizance of the risks of trauma and infection incidental to handling the large vessels when they, themselves, undertake such major procedures as lymphadenectomy.

Extension of surgical extirpation of a primary growth to removal of, first, the inguinal lymph nodes and, then, the pelvic nodes, is now an accepted practice, and it has been enabled by vast advances in surgical treatment. One wonders how much farther "cutting for cancer" will go.

It was not without very careful consideration that the accepted limits of surgical treatment of vulvar carcinoma were exceeded in this case, but the relative youth of the patient, the large size and prolonged history of the growth, confidence in the safety of modern surgical procedures to avoid shock and infection, and a hopeful confidence, perhaps quite misplaced, in concomitant sympathectomy as a means of lessening the chance of development of thrombosis and embolism, all were strong impelling influences.

It must be admitted that unilateral dissection of the lymph nodes in any region within the sphere of metastases of carcinoma of the vulva is at first sight unsatisfactory, but, in this case, because the lymph nodes in the inguinal and pelvic zones were free from cancer, it was felt that it was most unlikely that the left lumbar chain would be invaded. This conclusion, rightly or wrongly, was readily acted upon in view of the fact that retroperitoneal surgery of the glands and nerves is not frequently practiced.

Summary

1. One case of carcinoma of the vulva, occurring in a woman 37 years of age, for which wide vulvectomy, bilateral inguinal and pelvic lymphadenectomy and right lumbar lymphadenectomy and lumbar sympathectomy were performed, is described.

2. The reasons for performing lumbar lymphadenectomy and lumbar sympathectomy as a prophylactic measure and its method of performance are presented and discussed.

3. Similarly, the reasons and a method for extending lymphadenectomy in carcinoma of the vulva to include the lumbar glands are given.

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Discussion

DR. DANIEL MORTON, San Francisco, California.—It is fortunate that cancer of the vulva is one of the rarer types of pelvic malignancy, since the opportunity to treat it in an early stage presents itself rather infrequently. Furthermore, the treatment is by no means satisfactorily determined. Taussig's results, last reported in 1940 (at a meeting of this Society), are the best I know of. As you are well aware, he advocated complete vulvectomy plus bilateral resection of the superficial and deep inguinal nodes, the femoral nodes, and the obturator node, though he minimized the importance of the latter. Others have combined vulvectomy with x-radiation of the glands mentioned. Radiation of the local lesion has been used, and not without success, but produces so much havoc in the vulval skin that this method is usually reserved for inoperable cases. Few have followed a consistent policy, however, and incomplete operations are frequent. Taussig estimated that about 70 per cent of cases were operable. He found that approximately 40 per cent of his cases had regional gland involvement. He had five-year cures in 58.5 per cent of those completely operated upon, and 32 per cent of the total of 155 cases.

Now Dr. Robertson has devised an even more radical operation. There is no doubt that the more radical the procedure the greater will be the chance of eradicating all of the cancer. However, one finally reaches a point of diminishing returns. I believe that this is so for the operation described, at least in the usual case. While the removal of even isolated distant metastases is sometimes indicated and curative, cancer operations (any organ) which aim to remove glands much beyond the first line of defense (represented for the vulva by the inguinal and femoral glands) are rarely successful because (1) the mortality goes up, and (2) if second stage glands are involved, even more distant structures are also likely to be involved.

With regard to the mortality, it must be remembered that the majority of women with vulval cancer are rather old. While improved anesthesia and pre- and postoperative care will undoubtedly allow such a radical operation in most cases without immediate "on the table" mortality, these women are bound to be more subject to pneumonia, infection, and possibly to embolism.

It is possible that in occasional cases, e.g., in young women, as in the case described by Dr. Robertson, who would otherwise have a chance for many years of life, such an operation might be indicated. In this connection, one might consider the use of x-radiation which would certainly have as much rationale as its use in cervical cancer, so far as nodes are concerned. You may recall that we demonstrated a much lower incidence of glandular involvement in cervical cancer cases *after* x-radiation, than without it.

With regard to sympathectomy, I find myself unable to comment. I have had no experience along these lines. Offhand, I believe that I would rather fear the very complications which Dr. Robertson seeks to avoid, due to the necessarily rather rough manipulation of the vessels incident to sympathectomy.

I am unable to quarrel with Dr. Robertson for treating a case of vulvar cancer in a young woman in the way in which he has described. However, I do feel that such an extension of surgical maneuvers will rarely be indicated.

DR. LOUIS E. PHANEUF, Boston, Mass.—Dr. Robertson emphasizes earlier recognition of the lesion in carcinoma of the vulva in order to improve the results, and this is in accord with the recommendations of those interested in the treatment of cancer, no matter where situated. Dr. Robertson points out that more extensive surgery and heavier and wider irradiation may also give better results, with which I heartily agree. Modern technique and prep-

eration, as well as improved postoperative care, allow more extensive operations in the treatment of cancer, such as a radical operation, unthought of a quarter of a century ago.

In so far as carcinoma of the vulva is concerned, this condition is usually found in old people, a number of whom are poor surgical risks; it is, therefore, advisable to do the operation in stages. Some do the lymphadenectomy first and later the vulvectomy. Dr. Robertson starts with the vulvectomy and does the lymphadenectomy sometime later. Taussig popularized the Bassett operation in this country and made it the accepted method for treatment of carcinoma of the vulva. It is agreed by most gynecologists that in this particular disease, surgery is preferable to irradiation by means of radium and x-ray.

Dr. Robertson presents a case report of carcinoma of the vulva in a woman 37 years of age, on whom he performed a vulvectomy, inguinal, pelvic, and lumbar lymphadenectomy, and followed that by lumbar sympathectomy as a prophylaxis against arterial spasm, venous thrombosis, and excessive sweating, it being Dr. Robertson's belief that by preventing excessive sweating the flaps are more readily healed, and this subsequently proved to be the case. In the dissection of the inguinal and femoral glands the saphenous vein was ligated and cut. Dissection of the lumbar glands is a more extensive step of the operation and one with which I am not familiar. I have personally had no experience with lumbar sympathectomy in connection with the management of carcinoma of the vulva.

The sulfonamides and antibiotics in the prevention of infection play a role in the post-operative care of this lesion as they do in other types of surgery. Spinal anesthesia, followed by pentothal intravenous anesthesia, as employed in Dr. Robertson's case, should prove to be satisfactory, but my personal preference would be for continuous spinal anesthesia.

I would be interested in knowing the end-result of this extensive operation.

DR. ARTHUR H. CURTIS, Chicago, Ill.—May I ask Dr. Robertson if he uses dicumarol?

DR. ROBERTSON (Closing).—No, we do not use dicumarol. My experience with dicumarol postoperatively has not been disastrous, but we have experienced massive hemorrhage after its use in two cases, and therefore would not use it again. After this rather extensive discussion I think we would advocate against using any such drug unless forced to do so.

THE DETAILED ANATOMY OF THE PARAURETHRAL DUCTS IN THE ADULT HUMAN FEMALE*

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SKENE'S¹ historic presentation in 1880 established the clinical significance of the paraurethral ducts. Prior to that time the presence in the human female of a structure homologous with the prostate had been discussed since Galen² first, although incorrectly, described such an organ. The evidence that the paraurethral ducts and their glands are homologues of the prostate has come to be generally accepted. However, the extent and the detailed anatomy of these structures still remains a controversial matter, and a review of the present-day literature confirms Everett's³ statement that there is no unanimity of opinion on the subject of paraurethral and urethral glands. The purpose of this presentation is to describe the paraurethral ducts and glands of several adult human females as studied in serial sections and as demonstrated in wax model reconstructions in an effort to portray, at least in part, the anatomy of the prostatic homologue in the adult human female.

Galen, in describing the homology of the female genitals, mentioned a prostatic gland. However, it would appear from his description that he was not alluding to a gland about the urethra, but to some structure near the Fallopian tube. Interestingly enough Galen pointed out that Herophilus first had referred to the similarity of the male and female genitals. Riolan,⁴ in commenting on Galen's description, mentions that only Piccolomini's observations were in accord with those of Galen, and that other early anatomists disagreed with Galen's concept that a homologue of the prostate exists in the human female. de Graaf⁵ in 1672, gave the first description of glands and ducts about the female urethra. In "De mulierum organis generationi inservientibus" he described large ducts opening into the female urethra near the meatus and also above these ducts smaller crypts which drain the female prostate. In an illustration, de Graaf showed a glandular structure of considerable size surrounding the urethra with two ducts which are comparable to those described by Skene two centuries later. De Graaf called this gland with its ducts the female prostate. Sixty years later Astruc⁶ (1737), in a treatise on venereal diseases, described a prostate which surrounds the female urethra and also small lacunae along the sides of the urethral canal. Winslow⁷ (1775) mentioned smaller lacunae and one larger duct in the female urethra. Boyer⁸ (1797) described in some detail the openings of mucous secreting glands at the urethral meatus and in the urethral mucosa. Cruveilhier⁹ (1844) stated that there was no prostate in the female, but that there were numerous urethral mucosal crypts or lacunae opening into the urethral mucosa. In 1853 Virchow,¹⁰ in describing calculi he had noticed in the female urethral glands, alluded to these glands as homologues of the prostate.

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Robin and Cadiat¹¹ found no glands about the female urethra and doubted the existence of a prostatic homologue.

Skene's original description and its accompanying illustration are still the basis for most descriptions of paraurethral ducts in the current literature. In his original article Skene wrote: "Upon each side near the floor of the female urethra there are two tubules large enough to admit a No. 1 probe of the French scale. They extend from the meatus urinarius upwards from three-eighths to three-quarters of an inch . . . the tubules run parallel with the long axis of the urethra . . . they are located beneath the mucous membrane in the muscular walls of the urethra . . . the mouths of these tubules are formed upon the free surface of the mucous membrane of the urethra within the labia of the meatus urinarius. The location of the openings is subject to considerable variation according to the condition and form of the meatus. . . The upper ends of the tubules terminate in a number of divisions which branch off into the muscular walls of the urethra."

Following Skene's description, the origin and even the presence of urethral ducts and glands came in for considerable discussion. To some extent this discussion has persisted to the present time. In 1889 Tourneaux¹² pointed out that the urethral glands of the female, together with the paraurethral ducts, are homologues of the prostate. Oberdieck¹³ and later Aschoff¹⁴ found deep prostaticlike lacunae along the female urethra. Felix¹⁵ considered the paraurethral glands to be prostatic homologues. In 1901, Pallin¹⁶ pointed out that the glands of the female urethra were homologous with that portion of the prostate arising cephalad to the urogenital sinus. In 1911, Wyatt¹⁷ concluded that the glands surrounding the female urethra are prostatic homologues, and that the female urethra is a counterpart of the male prostatic urethra. Johnson,¹⁸ in 1922, after constructing wax models of several embryonic urethras, felt that the paraurethral ducts are unquestionably homologous with male prostatic ducts.

Hunner¹⁹ described the openings of numerous mucous glands along the inferior urethral wall and noted that the glands tend to increase in size and complexity toward the outer end of the urethra. He quoted Schuller²⁰ as having found a third but smaller gland or tubule lying in the midline between the two described by Skene.

In recent years interest has been renewed in this problem, and some disagreement has occurred relative to the presence of urethral glands, other than Skene's ducts, and as to their extent and importance. Deter, Caldwell, and Folsom²¹ have presented evidence that there are tubular glands about the posterior urethra and that they are clinically important in urethral disease. MacKinsie and Beck²² after examining numerous longitudinally sectioned urethrae of children and adults reported that true urethral glands do not exist in that third of the urethra nearest the bladder. They found that while the paraurethral glands may encircle the urethra they drain only through openings on the urethral floor. According to MacKinsie and Beck, true periurethral tubular epithelial structures appear in the anterior two-thirds of the urethra adjacent to the compound racemose glands of Skene. These, they feel, are distinct from Skene's ducts, are not always present, and are less frequent in the middle third of the urethra. Cabot and Shoemaker,²³ after studying a number of female urethras cut in longitudinal section, came to the conclusion that there are no important gland structures in the proximal two-thirds of the female urethra, and that glands of the female urethra—except Skene's glands—do not play an important role in infections of the female urinary tract. These authors observed

a number of very deep crypts in the urethral mucosa which, running for some distance, might be mistaken for glandular structures if care was not exercised in examining the arrangement of the cells; they state, however, that careful study will show that these crypts are not glands but simply invaginations of the mucosa. Cabot and Shoemaker further described cysts and cell nests in the mucosa and submucosa of the urethra which they believed were derived from von Brunn's cell rests; they did not believe these structures were of notable clinical significance.

The embryologic development of the glandlike tubules about the female urethra has been described by Phallin, Wyatt, Johnson, and me. The *analgen* of these glands arise for the most part entirely above the müllerian tubercle and first appear in the 50 mm. fetus as solid buds protruding from the ventral and lateral sides of the urethra. Branched glands are present in the 128 mm. fetus. Embryologically they are homologous with that portion of the prostate which is cephalad to the prostatic utricle. From the material previously reported,²⁴ it appears that the larger paraurethral ducts and their glands arise from *analgen* above the Müllerian tubercle, that they are identical with the other urethral glands in origin and structure, and that they, like the other tubules emptying into the urethra, are homologous with that portion of the prostate which develops above the union of the mesonephric ducts with the urogenital sinus.

The material for this study was obtained from eleven necropsies. From each a mass of tissue was excised which contained the entire urethra and the surrounding structures lying beneath the pubic arch, the lower portion of the bladder, and the anterior vaginal wall. After fixation each mass was cut to a size suitable for histologic preparation. When so trimmed, each block consisted of the urethra, the periurethral tissues, and the intact suburethral vaginal mucosa. These blocks were then cut transversely into several serial blocks and, subsequently, each block was serially sectioned at 10 micra. Every twenty-fifth section was stained with hematoxylin and eosin. When wax models were to be made these sections were placed under a projecting microscope and enlarged. The enlarged images were transferred onto paper, the outlines of the desired structures were traced, and they were transferred from the paper onto wax plates whose thickness was such as to maintain correct longitudinal proportions. The serial wax plates were subsequently annealed to form models.

Fig. 1.—Drawing of wax model (Model I) of an adult human female urethra with its paraurethral ducts and glands as seen in right lateral view. This reconstruction is in reality a cast of the urethral canal with its outpouching ducts and glandular pockets. The base of the model labelled "Vaginal canal" represents a cast of that portion of the vagina which is beneath and parallel to the urethra. The smaller diagrams demonstrate transverse sections through the urethra, the paraurethral ducts and glands, and the vaginal canal beneath the urethra at different levels above the meatus. Tissues from which this model was reconstructed were obtained at necropsy of a 20-year-old virgin. This model represents the distal 2.4 cm. of a urethra which had a total length of 2.8 cm. It will be noted that no paraurethral ducts open at or immediately within the urethral meatus. Thirty-one ducts empty into this urethra. Although most of these ducts empty into the distal third of the urethra (Fig. 3), several others empty into the middle and proximal thirds. After leaving the urethra the ducts turn cephalad and extend parallel with the urethral canal. One large duct on the right develops into a cyst of considerable size. At the midpoint in the urethra many ducts and glands extend laterally far from the canal; at a more proximal level the urethra is surrounded by many small tubules, and on the right it is encompassed by a thin compact semi-circular sheet of ducts and glands (See Fig. 6).

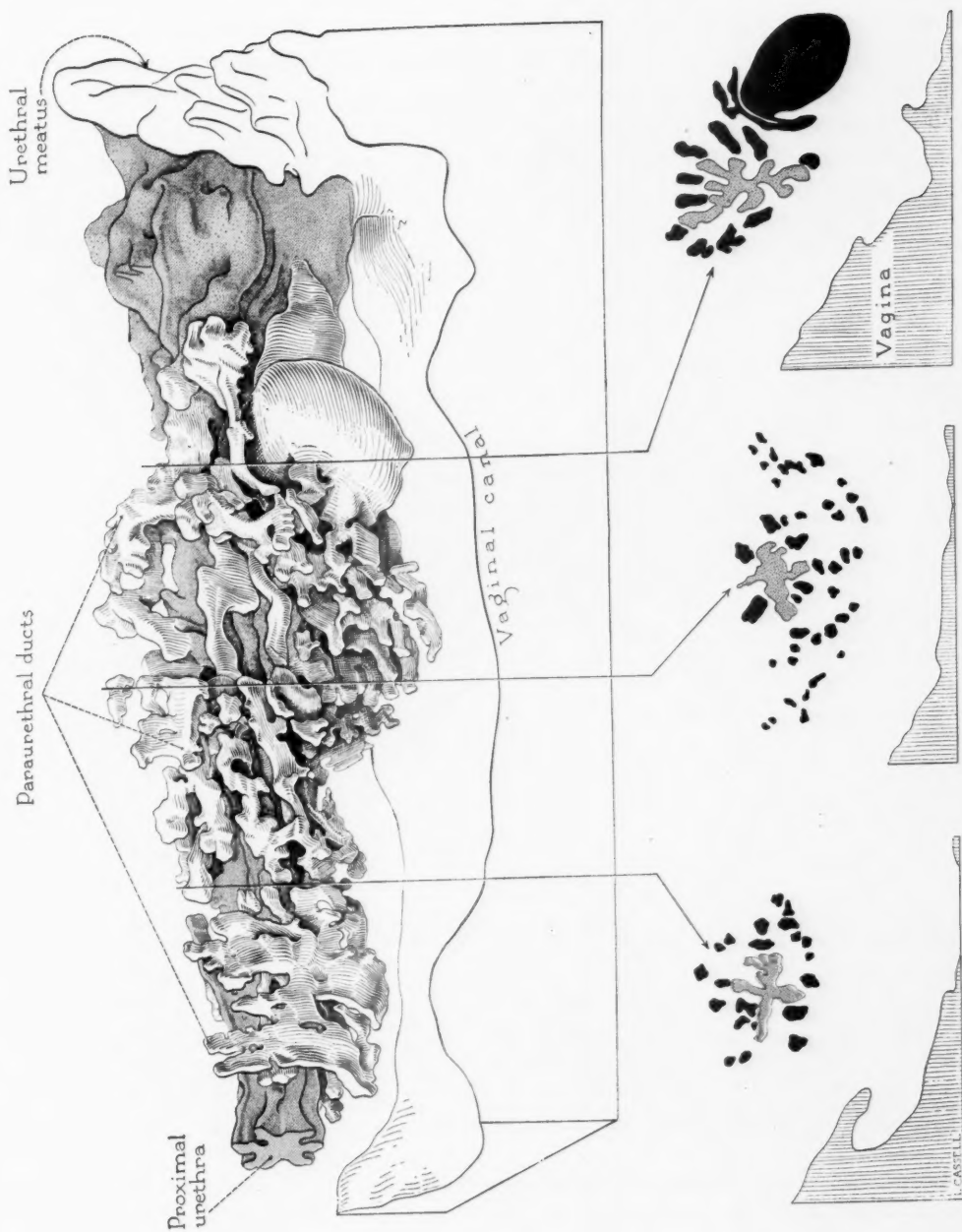


Fig. 1.—(For legend see opposite page.)

During vaginal examinations ductlike openings just outside and dorsal to the urethral meatus are frequently noted. Occasionally these are the mouths of minor vestibular glands; more often they are entrances of paraurethral ducts. They are usually seen in multiparas, and their location may result from distortion which was a concomitant of labor and which produced a flattening of the urethral eminence with eversion of the distal urethral mucosa. In women who have not borne children, the urethral labia are ordinarily well formed, the urethral mucosa is not everted, and the openings of the paraurethral ducts are usually not visible until the urethral labia are separated and the outermost mucosa exposed.

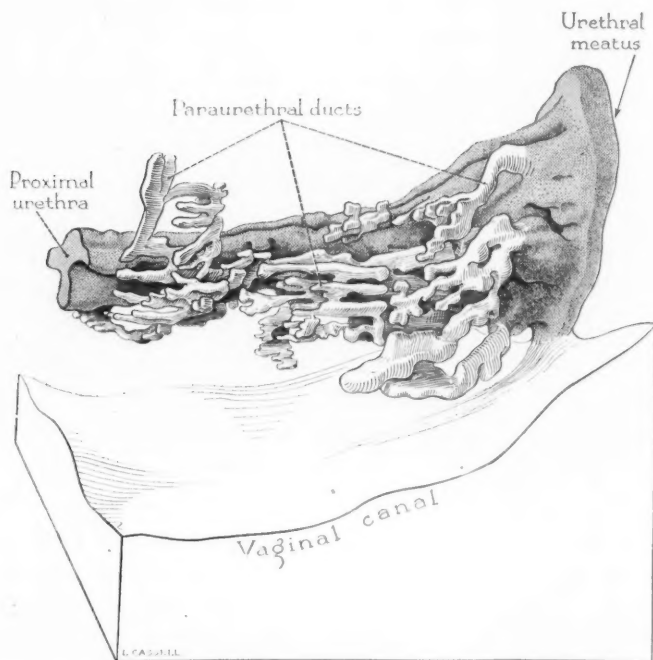


Fig. 2.—Drawing of a wax model (Model II) of an adult human female urethra with its paraurethral ducts and glands as seen in right lateral view. This reconstruction is in reality a cast of the urethral canal with its outpouching ducts and glandular pockets. That portion of the model labelled "Vaginal canal" represents a cast of the vagina beneath and parallel to the urethra. Tissue from which this model was reconstructed was obtained at necropsy of a 38-year-old nullipara. This model represents the distal 2.8 cm. of a urethra measuring 3.0 cm. in total length. No ducts opened at the meatal margins. In this specimen most of the ten larger paraurethral ducts empty into the distal centimeter of the urethra through the lateral and dorsal walls. (See Fig. 3.) Occasional ducts empty also into the most distal portion of the middle third of the urethra. Most of the ducts and glands are noted in the lateral and dorsal periurethral tissues. About the middle third of the urethra, the paraurethral ducts and glands are found far from the urethral canal and, as in Model I (Fig. 1) form semicircular sheets about both the right and left sides of the urethra.

Study of serial sections from all specimens and examination of reconstructions of three urethras (Figs. 1, 2, and 4) reveal certain characteristics that are common to all. In each of them the urethra immediately within the meatus is slitlike with the long axis lying ventrodorsally. The most distal paraurethral ducts open into the canal just within the meatus and extend outward from the urethral mucosa into the dense connective tissue which makes up the urethral wall. This wall is surrounded by and is an integral part of the dense connective

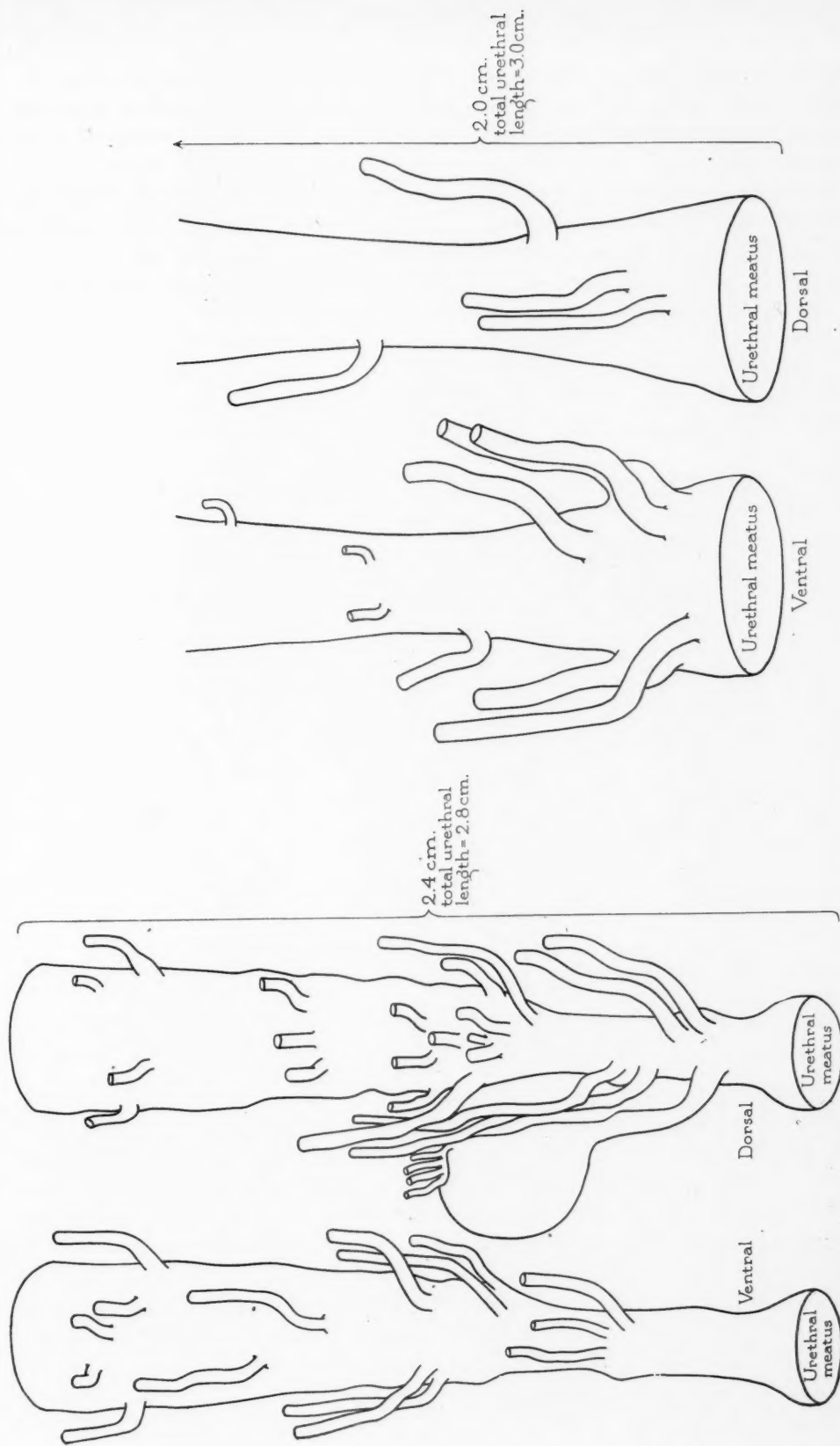


Fig. 3.—Diagrams of Models I and II as viewed dorsally and ventrally to demonstrate the distribution of the paraurethral ducts. The terminal portions of the ducts and the glands are not shown. It will be noted that most of the ducts empty into the distal one-third of the urethra through the dorsolateral and ventrolateral walls.

tissue shelf (the urogenital diaphragm) lying beneath the vaginal mucosa. Infections in the larger of these most distal paraurethral tubules first attracted Skene's attention and led him to describe the structures which have since borne his name.

In all specimens the greatest number of paraurethral ducts empty into the distal one-third of the urethral canal. (In two all duct orifices are in the distal centimeter of the urethral canal; in six the duct openings are limited to the distal 1.5 cm., with most of them near the meatus; in three specimens occasional

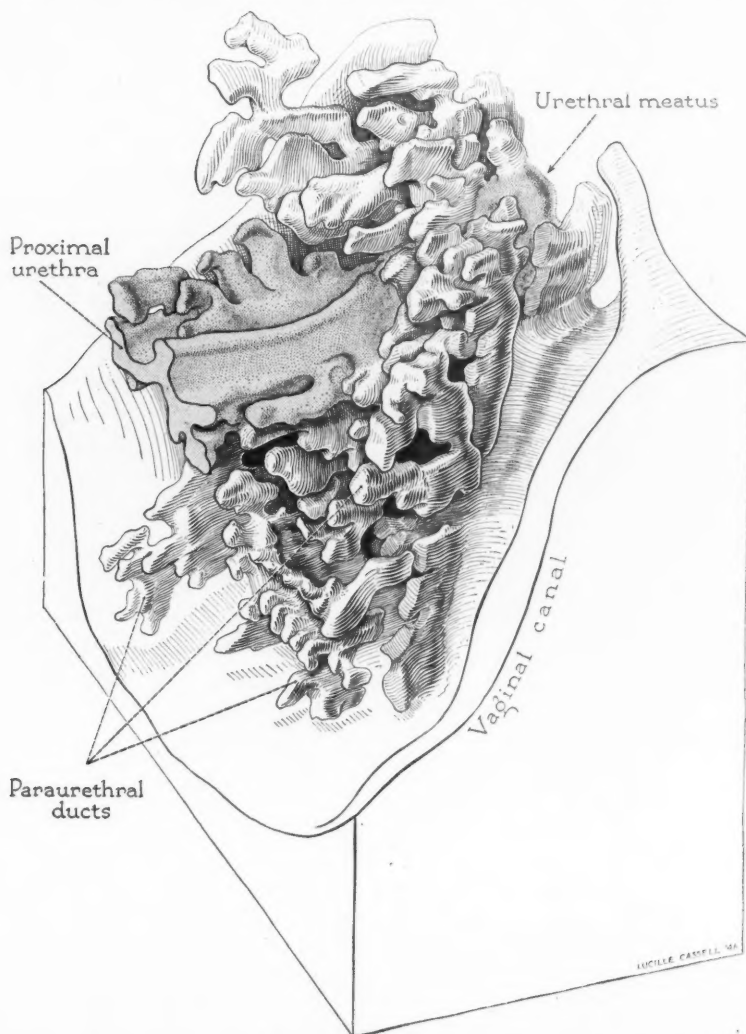


Fig. 4.—Drawing of a wax model (Model III) of an adult human female urethra with its paraurethral ducts and glands as viewed ventrolaterally from the right side. This reconstruction is in reality as cast of the urethral canal with its outpouching ducts and glandular pockets. That part of the model labelled "Vaginal canal" represents a cast of the vagina beneath the urethra and parallel to it. This model is a reconstruction of tissue which was obtained at necropsy of a 32-year-old virgin; it represents the distal 0.8 cm. of a urethra measuring 3.4 cm. in total length. No ducts or glands of appreciable size were found above the level shown in this specimen. No ducts empty outside of the meatus, and none of the ducts measure more than 4 cm. in length. Twenty separate ducts can be identified; these are arranged in four major groups of which two groups empty into the dorsolateral, and two groups into the ventrolateral urethra immediately within the meatus. At the terminations of these tubules there is a marked proliferation of glandular tissue which surrounds the urethra on all sides.

tubules open into the urethral canals throughout most of their lengths) (Fig. 3). There is a definite tendency for the mouths of the ducts to be in four groups (Fig. 4) with two groups on each side, i.e., on each side there is a ventrolateral group and a dorsolateral group. When larger tubules are present they are usually in the dorsolateral location. In addition to these major groups there is, however, a considerable number of ducts opening into the lateral, the dorsal, and a few in the ventral urethral walls. After leaving the urethral canal these tubules turn cephalad and promptly divide into small branches (Fig. 5). These small branches wander outward in the lamina propria away from the urethral canal; they tend to pursue a course somewhat parallel with the urethra itself, and often extend cephalad for a considerable distance. It is not unusual for a single specimen to have a number of these ducts each of which with its branches and glands has an over-all length of from 0.7 to 1.2 centimeters.

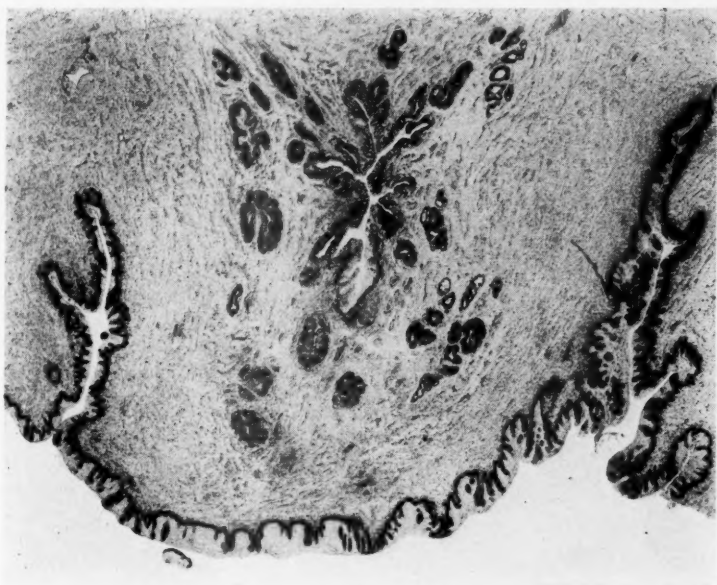


Fig. 5.—Photomicrograph of a transverse section through the urethra just within the meatus (Model III) showing the urethra surrounded by many paraurethral tubules and glands. The intact vaginal mucosa borders the lower edge of the section.

More deeply within the urethra the number of paraurethral ducts opening into the urethral canal becomes less. However, in the more cephalic sections the dissemination of ducts, terminal tubules, and glands away from the urethral canal and into the urethral wall is greater. At these levels the smaller branches of the larger ducts which have emptied into the more distal urethra terminate in multiple small budlike out-pocketings and tubular glands. These terminal structures are noted for the most part in the lateral and inferior urethral walls, but each specimen shows a considerable number of ducts and small tubules spreading ventrolaterally and ventral to the urethral canal. This collection of ducts and glands forms a labyrinthlike mass dorsally and laterally which, when indurated by inflammation, produces the thickening so commonly felt after urethral infections.

In some specimens at higher levels the urethra is surrounded on all sides by many small tubular buds and glands which extend to the outermost limits of the connective tissue core making up the urethra itself. Dorsally, they may closely approach the vaginal mucosa. Lateralward, far from the meatus, at the cephalic end of the gland mass, and well away from the urethral canal, the terminal tubules and terminal glands frequently form thin semicircular masses which lie in the lines of stratification of the fibers of connective tissue encircling the urethra (Fig. 6).

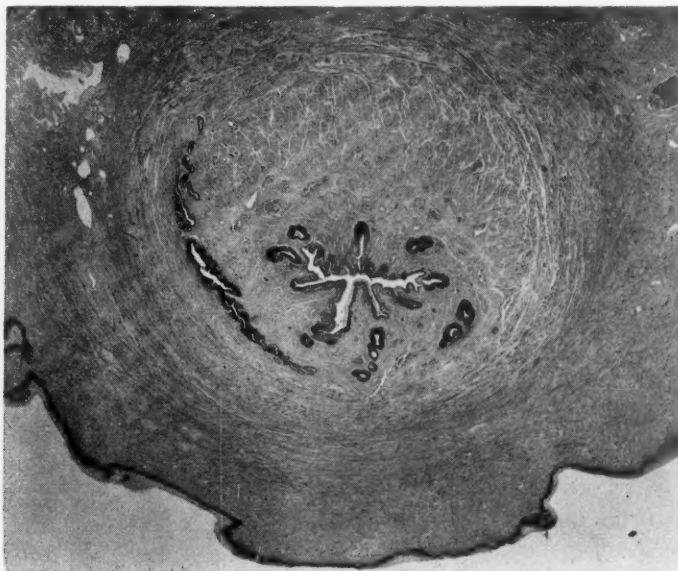


Fig. 6.—Photomicrograph of a transverse section through the urethra and periurethral tissues (Model I) to demonstrate the widespread of paraurethral ducts and glands away from the urethra. In this section (approximately 2.1 cm. proximal to the meatus and 0.5 cm. from the bladder) the paraurethral structures form a thin semicircular mass lying in the fibers forming the urethral wall. The intact vaginal mucosa borders the lower edge of the section.

In the material studied the presence of two large lateral ducts as described by Skene was the exception rather than the rule, and the widespread branching of the terminal divisions was more marked than Skene described. In but two of eleven specimens could two larger tubules, one on each side of the urethra, be followed for any distance. Except for their greater diameter and longer length, these tubules resembled the other paraurethral ducts seen in the same specimen and in other specimens; they were lined by the same type of epithelium and terminated in tubular glands just as the other ducts described herewith. The least number of ducts found in any of the urethras examined was six, the most thirty-one.

Paraurethral glands have, in the past, occasionally been referred to as compound racemose or racemose structures. According to commonly accepted terminology "compound racemose" implies a number of branching ducts with numerous acini grouped about the termination of each duct, as in the major vestibular and parotid glands. The architectural pattern of the paraurethral

glands does not correspond with this description. They are branched tubular glands (Fig. 7), with straight or slightly curved branches, which empty into the paraurethral ducts. They are lined for the most part by columnar epithelium which is made up of cells varying from low columnar, approaching cuboidal,

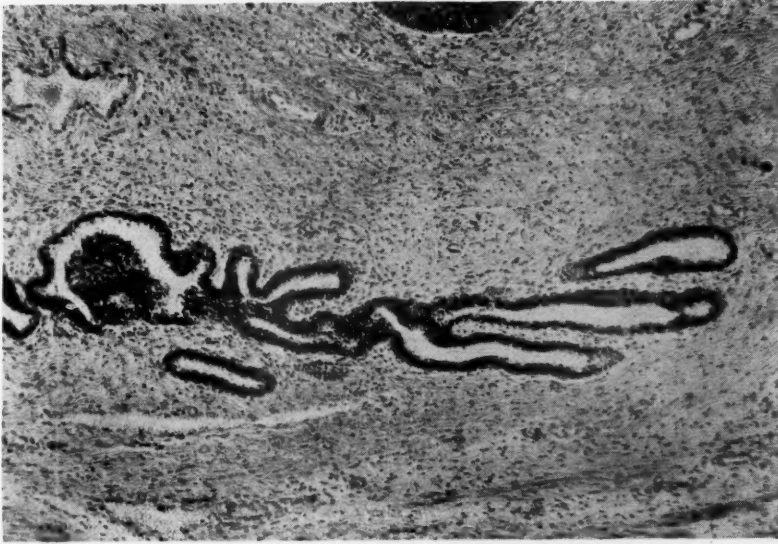


Fig. 7.—Photomicrograph. The paraurethral ducts terminate in branched tubular glands and arborescent tubular pockets.

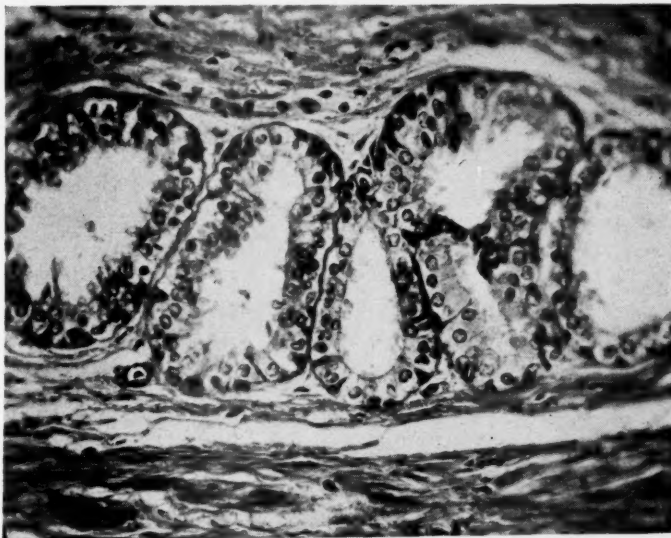


Fig. 8.—Photomicrograph. The tubular paraurethral glands are lined by low columnar epithelium with pale staining cytoplasm and have large centrally or basally placed round nuclei; some but not all of these cells take a mucicarmine stain.

to moderately tall cylindrical cells (Fig. 8). There are occasional nests of mucous secreting cells within this columnar epithelium. These cell nests have a definite secretory activity as demonstrated by mucicarmine stain. Not all

branches of the ducts, however, terminate in glands; many end in small pockets, tiny dilated cystic spaces, and minute arborescent tubules which are lined by a pseudostratified columnar epithelium several times thicker than the lumen of the tubule itself. Infrequent intraepithelial glands of mucous secreting cells are found within this epithelium (Fig. 9).

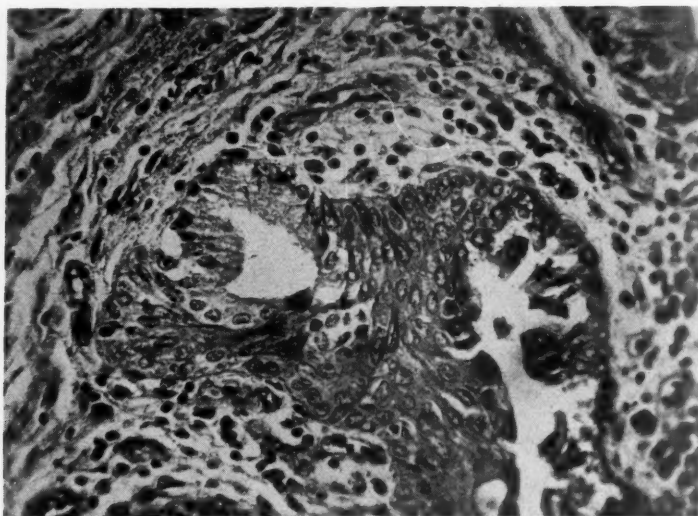


Fig. 9.—Photomicrograph. Infrequent intraepithelial glands of mucous secreting cells are found in the walls of the paraurethral ducts. They take a mucicarmin stain.



Fig. 10.—Photomicrograph of a section in which a small paraurethral duct empties into the urethra. The duct near the urethra is lined by squamous epithelium; more deeply the lining is pseudostratified columnar epithelium.

Most of the smaller and many of the larger branches of the paraurethral ducts are also lined by pseudostratified or true stratified columnar epithelium (Fig. 10). Near their orifices the lining of the ducts becomes the same type as

that of the urethra at that level, i.e., stratified squamous epithelium lines the ducts which empty nearest the meatus; the ducts which open into the midurethra are lined by transitional epithelium which frequently also comprises the urethral mucosa at that level.

Cystic dilatation of the ducts is apparently common, as it was seen in several specimens; these dilatations occurred most often in the terminal portions of the tubular branches. One such cyst was larger than the adjacent urethra. These cysts are lined by thinned out, flattened epithelium of the same type as that of the duct. Some contain an amorphous material which does not take a mucicarmine stain. Inflammatory reactions in and about the ducts and glands is common. Round cell and leucocytic infiltration has been observed beneath the epithelium, and minute localized abscesses and inflammatory destruction of the duct wall has been noted in several instances.

Comment

The definition of the *ductus paraurethrales* in the Basle anatomic nomenclature is "the ducts of Skene's (paraurethral) glands, opening in the vestibule of the vagina on either side of the urethral orifice."²⁵ The definition of the *glandula paraurethralis* as adopted by the Committee on Nomenclature of the German Anatomical Society is "one of a number of mucous glands (Skene's glands) in the wall of the female urethra." The term "periurethral" glands has also been frequently used for the same structures, although the term is not found in standard medical dictionaries.

The structures as described here are neither *paraurethral* (para-meaning "near, alongside of, a departure from the normal") nor are they *periurethral* (peri-meaning "around or about"). They lie not only alongside and near the urethra, but they are also about and around it, and they empty into it.

The name *prostatula muliebris* is present in the dictionaries where it is used as a definitive term for "spongy tissue at the orifice of the meatus urinarius in the female." On the basis of the homology it might be used anatomically for these ducts and glands. Historically de Graaf, Astruc, and Virchow used this descriptive term; more recently it has been suggested again by Korenchevsky.²⁶

Time, custom, and well-deserved recognition for outstanding clinical investigation have associated Alexander Skene's name with the paraurethral ducts. It is fitting that it should be perpetuated; however, it would appear proper to enlarge Skene's description to include the many other large ducts and their glands which are present in most individuals and which are identical with the two which he described.

The most striking finding in this study was the great extent of the tubules and epithelial lined pockets which lie about the adult human female urethra. It is correct to assume that the majority of us have considered this homologue of the prostate to be at best a scattering of insignificant tubules or evaginations on the floor of the urethra with two or occasionally three major ducts opening at the urethral orifice and extending laterally and dorsally in the urethral walls. Instead, the prostatic homologue is most often a widespread branching of ductal channels and glands surrounding the female urethra to some extent on all sides,

most notably laterally and posteriorly. The urethra might well be compared to a tree about which and growing outward from its base are numerous stunted branches, the paraurethral ducts and glands.

The marked variation in the extent of the paraurethral ducts in different individuals is also of interest. These structures usually do not surround the urethra in its entire length; commonly they are limited to the outer half. They may, however, extend along the distal two-thirds or more of the urethral canal reaching to within a few millimeters of the bladder. In some individuals they form a labyrinthine mass encircling the urethra on all sides, in others they lie almost wholly laterally and posteriorly.

While discussion concerning the nature of the gland-like tubules about the proximal urethra is not pertinent to this presentation, certain observations are of interest. There are many small glandular elements to be found about the upper one-half of the urethra. They are evident in transverse sections where they are most often seen laterally far from the urethral canal; they are the terminal glands of the ducts which empty into the urethra at a more distal point. Transverse serial sections show that the crypts and lacunae of that portion of the proximal urethra above the large ducts and their glands and near the bladder are lined by the same type of epithelium as that which lines the terminal glands and tubules of the paraurethral ducts. Furthermore, there are areas of infolding or invaginations of the urethral mucosa which are also lined by a similar type of epithelium. It would appear that most of these crypts, lacunae, and invaginations are diminutive developments from the same embryologic source as are the larger structures found more distally. Some of these lacunae have lumina and subdivisions comparable to their larger counterparts. In other words, the proximal urethra has rudimentary glands of exactly the same type as the larger glands found in the distal urethra. There seems every reason to believe that inflammation, irritation, and obstruction may result in the development of cystic enlargements of the intraepithelial glands and small submucosal lacunae of the proximal urethra as MacKinsie and Beck postulated in explaining the cysts which are sometimes found about the upper third of the female urethra.

The role of the paraurethral ducts in gonococcal infections of the female genitals is too well understood to require comment. Dr. Arthur Curtis has pointed out the value of palpating bristlelike thickening of the posterolateral ducts as pathognomonic evidence of a previous gonorrheal infection. That these ducts may be involved in other types of urethritis is less commonly realized. I have seen several women traumatized by catheterization who have subsequently developed a granular urethritis and in whom a marked induration (or periurethritis) of the posterior and lateral periurethral tissues strongly suggested involvement of the paraurethral ducts and glands.

Obstruction of the narrow outlet of infected paraurethral ducts is an important factor in the etiology of abscesses of the anterior vaginal wall. These abscesses may reach considerable size and extend along the fascial planes between the urethra and the vagina. Paraurethral abscesses of small size may also form in the urethral wall itself and eventually rupture into the urethra with the formation of a urethral pocket that ultimately, due to repeated infec-

tion, obstruction, and poor drainage, enlarges sufficiently to become a urethral diverticulum.

Years ago Routh²⁷ noted that the urethral glands may become retention cysts by obstruction of their orifices through urethritis or periurethritis. As a result of suppuration or rupture, the cyst then opens again into the urethra and the inflammation continues. Urine finds access to the diverticular cavity at each urination and, owing to the small caliber of the opening, the distention of the cavity increases. It is undoubtedly true, as is often asserted, that the trauma resulting from pressure of the fetal head on the dorsal urethral wall may be sufficient to rupture the urethral musculature with the production of a urethral diverticulum at the time of labor. It seems more likely, however, that this trauma would produce a widespread tearing of the urethral walls and supports with the formation of a urethrocele rather than a minute hernial aperture through which a finger-like pouch of mucosa would protrude.

Cysts of the anterior vaginal wall and suburethral tissues are moderately frequent. While of interest, they rarely become large enough to concern the patient. Cullen²⁸ felt that vaginal cysts rarely, if ever, originated from urethral glands. He noted that a connecting link with the urethra is usually lacking in such cysts, and that origin from Gartner's ducts seemed more likely. In view of the present demonstration of the anatomy of the paraurethral glands, and the knowledge that they may extend into the deeper suburethral tissues, it seems quite possible that retention cysts of such structures might equally well cause cystlike tumors of the anterior vaginal wall. Cystic dilatation of the ducts and glands is common; frequently they are connected to a duct by a narrow epithelial channel which would be impossible to demonstrate at the time of surgical removal. The usual location for Gartner's ducts is in the lateral or anterio-lateral vaginal wall, and the presence of a duct remnant in the midline beneath the urethra would presume its deviation from a normal anatomic location.

Primary carcinoma of the female urethra is infrequent. Most of the reported cases are an epidermoid type of growth; adenocarcinoma is rare.²⁹ Most of the few adenocarcinomas are described as hard, rounded, nodular masses surrounding the urethra and without ulceration of the urethral mucosa. Whitehouse³⁰ states dogmatically that such adenocarcinomas originate in the paraurethral glands and are homologous to prostatic carcinomas of the male. Menville³¹ points out that the majority of early carcinomas of the urethra arise near the meatus and that a paraurethral duct emptying near the external urethral orifice where it is susceptible to infection and trauma may be a frequent site for a primary growth. Since the paraurethral structures contain intraepithelial mucous secreting glands and true branched tubular glands, it is understandable that adenocarcinomas may occasionally develop from them.

The channels of the paraurethral ducts have been shown to reach the outermost limits of the urethral core. Trauma to or severance of such a channel may explain some of the heretofore inexplicable urethral fistulas developing after an apparently perfectly performed urethrocele repair. In a like manner, an urethro-vaginal fistula may follow a paraurethral duct abscess which communicated with both the urethra and the vagina.

Summary

The material studied consisted of serial sections and wax model reconstructions of adult human female urethras. As a result of this study, a concept of the anatomy and histology of the paraurethral ducts is presented. It would appear that these ducts are not constant in number or location; that they not only form extensive ramifications throughout the tissues about the distal urethra, but that they may also extend to within a short distance of the bladder; and that the often numerous ducts terminate in tubular glands which are lined for the most part by columnar epithelium. This epithelium has some, although limited, secretory activity.

The role which the paraurethral ducts may play in the etiology of lesions of the urethra and anterior vaginal wall is discussed.

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Discussion

DR. HOUSTON EVERETT, Baltimore, Md.—The method of approach which Dr. Huffman has adopted, namely the construction of wax models from serial microscopic sections, is one which among embryologists and students of the details of the more minute anatomic structures is considered practically infallible. I believe, therefore, that we may accept his work as the last word in the anatomy of these glands or ducts associated with the female urethra.

Previously there has been considerable confusion upon this subject, and eminent authorities have differed widely, some claiming that, aside from Skene's glands, there are no glands worthy of the name associated with the female urethra. Others have described numerous paraurethral glands which they have considered as homologous to the male prostate. If I interpret Dr. Huffman's findings correctly, they result in some approximation between these previously considered opposite points of view. In other words, most of the glands he described might be considered as part of the Skene's duct system, as their main ducts tend to enter the urethra in its lower portion, but on the other hand this makes of this system a considerably more elaborate and complex one than the two paraurethral ducts originally described by Alexander Skene.

From the clinical point of view, gynecologic interest in the paraurethral glands was chiefly concerned with the fact that Skene's ducts often became involved in gonorrheal infections. This usually resulted in a chronic gonorrheal urethritis which was intractable to treatment until the focus of infection in these tiny glands was eradicated. The modern chemotherapeutic and antibiotic methods of treating gonorrhea have gone far in reducing the incidence of this phase of the disease. However, it is quite probable that deep-seated infection of a nonspecific nature in these glands may play an important role in the so-called nonspecific or granular urethritides, which often prove to be an exceedingly difficult therapeutic problem. That these glands are important factors in the production of suburethral abscesses, cysts, and diverticula, it seems to me is hardly open to doubt.

I rather wish that Dr. Huffman had not found it so convenient to apply the term *female prostate* to the group of glands under consideration. This is not a new concept, and this anatomical concept in the past has led, upon the part of certain eminent urologists, to an overly enthusiastic adoption of the clinical concept of *female prostatism*. This idea in turn has resulted in the too frequent use of the cautery punch or resectoscope on the female vesical orifice. Upon the basis of what I believe would be considered a rather large experience in dealing with female urological patients, I am thoroughly convinced that obstructions at the vesical neck sufficient to produce residual urine or retention of urine rarely occur in the female from causes in any way simulating prostatism in the male. Furthermore, I am convinced that the use of the cautery punch or resectoscope on the vesical neck of the female carries with it certain dangers of intractable sphincter incompetence or even vesicovaginal fistula. As it usually falls to the lot of the gynecologist to correct such defects, they are probably much more seriously appreciated by the gynecologist with an adequate urological experience than by a urologist with little or no experience in gynecology.

DR. ARTHUR H. CURTIS, Chicago, Ill.—Despite the fact that I went over Dr. Huffman's paper with painstaking care and approved of it as it was to be presented, I am heartily in accord with Dr. Everett's objection to calling this glandlike tissue the female prostate. Anatomically, it is probably analogous, but "female prostate" is an unfortunate name to use. There must be no implications which may tempt clinicians to resort to surgical extirpation.

DR. HUFFMAN (Closing).—Dr. Everett and Dr. Curtis have pointed out the error of my ways in using the term "female prostate." I think that perhaps I was guilty of placing too much emphasis on the embryology of the paraurethral ducts and glands. They are of course homologous with the prostate, but I can see where it would perhaps be better not to use the term "female prostate," at least in clinical medicine.

CULDOSCOPY, A USEFUL GYNECOLOGIC PROCEDURE*

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FOR a period of years our clinic has been interested in visualizing the pelvic organs in selected cases by means of the peritoneoscope. In many instances we found peritoneoscopy to be a very useful procedure and sufficient additional information often was obtained to save the patient an exploratory laparotomy. In other cases the necessity of surgery became apparent on gaining further information by visualization of the pelvic organs. Useful as peritoneoscopy was, it often left something to be desired. The peritoneoscope entered the abdominal cavity at a considerable distance from the pelvic viscera, and the tip of the instrument often had to find its way through many loops of small intestine before the pelvic region was reached. Not infrequently these loops of bowel were troublesome. Still more troublesome were adhesions from previous operations and at times they made visualization of the pelvic viscera impossible. It occurred to one of us (R. W. T.) that a better and more direct approach to the pelvic organs could be made through the posterior vaginal fornix, and in 1940 such an attempt was made by means of the peritoneoscope with the patient in the lithotomy position. Air was introduced by means of a bulb as in the ordinary transabdominal peritoneoscopy. It was found to be impossible to retain enough air in the peritoneal cavity to prevent the intestines from interfering with visualizing the pelvic viscera. This was due to the fact that the thin vaginal wall failed to grip the peritoneoscope as snugly as the abdominal wall. It remained for Decker to grasp the advantage of the knee-chest posture as a means of sucking air into the abdomen, just as in the air method of cystoscopy. Decker has published four articles on the subject of culdoscopy which are the only ones we have been able to find in the literature.

During the last year we have made frequent use of the culdoscope, and have come to regard it as a valuable diagnostic aid. This paper is a report of our experience in 56 cases.

The Instrument.—Since it is possible that some are not familiar with the culdoscope, the apparatus is pictured in Fig. 1. There is a special trochar with a guard on the sheath about 3 cm. from the tip to prevent introduction of the trochar too far. A valve is attached near the head of the sheath through which CO₂ gas can be introduced into the peritoneal cavity. We have never made use of this, since the results with air have been quite satisfactory. The trochar proper can be fixed in the sheath by means of a special locking device at the head of the sheath. The culdoscope proper consists of a longer metal tube with ocular and objective lenses with a prism to deflect the light so as to

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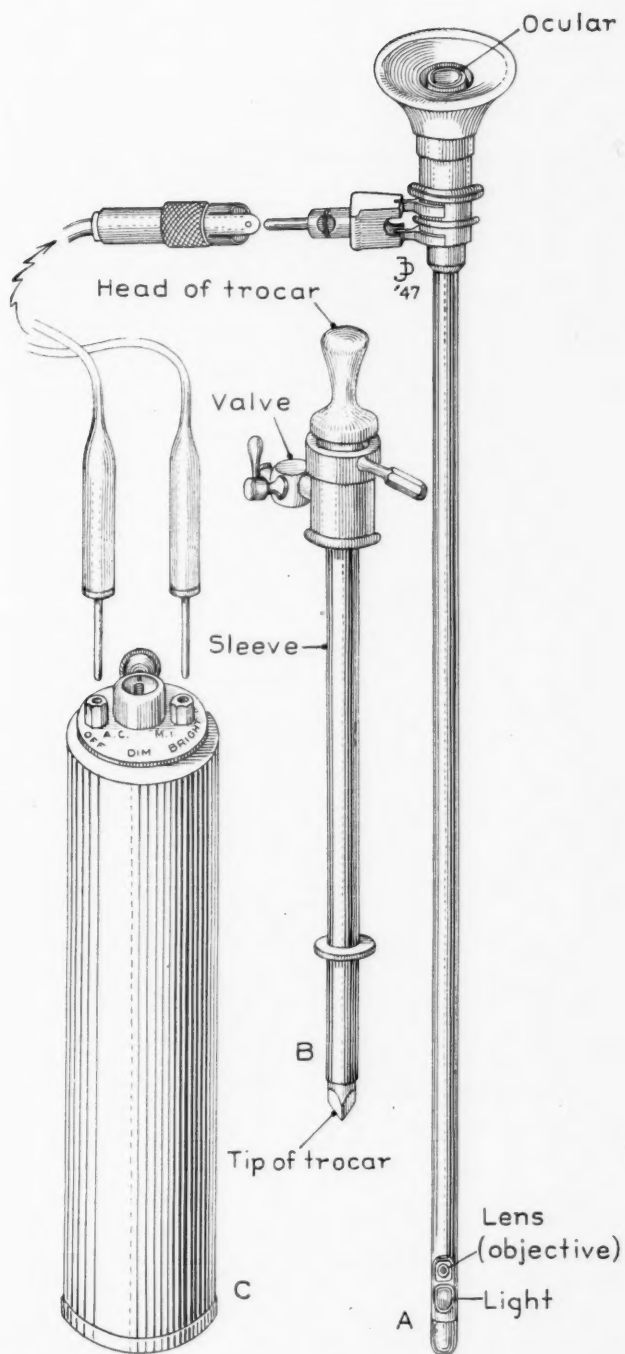


Fig. 1.—Culdoscope. Description of instrument is found in the text.

make the abdominal contents visible through the ocular. Just distal to the objective lens is a small electric bulb which is illuminated by means of a dry cell battery. The one pictured in Fig. 1 is the one supplied by the manufacturers, but we have made a larger one which gives better illumination.

The Procedure.—The patient is placed in the knee-chest posture. Various devices have been designed to hold patients in the knee-chest position, but for the most part they appear to be of more trouble than value. If the culdoscopic examination is to be made with the patient awake, she can maintain the position unsupported for a time sufficient to permit completion of the examination. If the examination is to be made under general anesthesia, she can be held in position quite satisfactorily by an intern or nurse standing on either side of her with the adjacent arm encircling the patient's thigh. If the patient is in proper position she need only be kept in balance which requires very little effort.

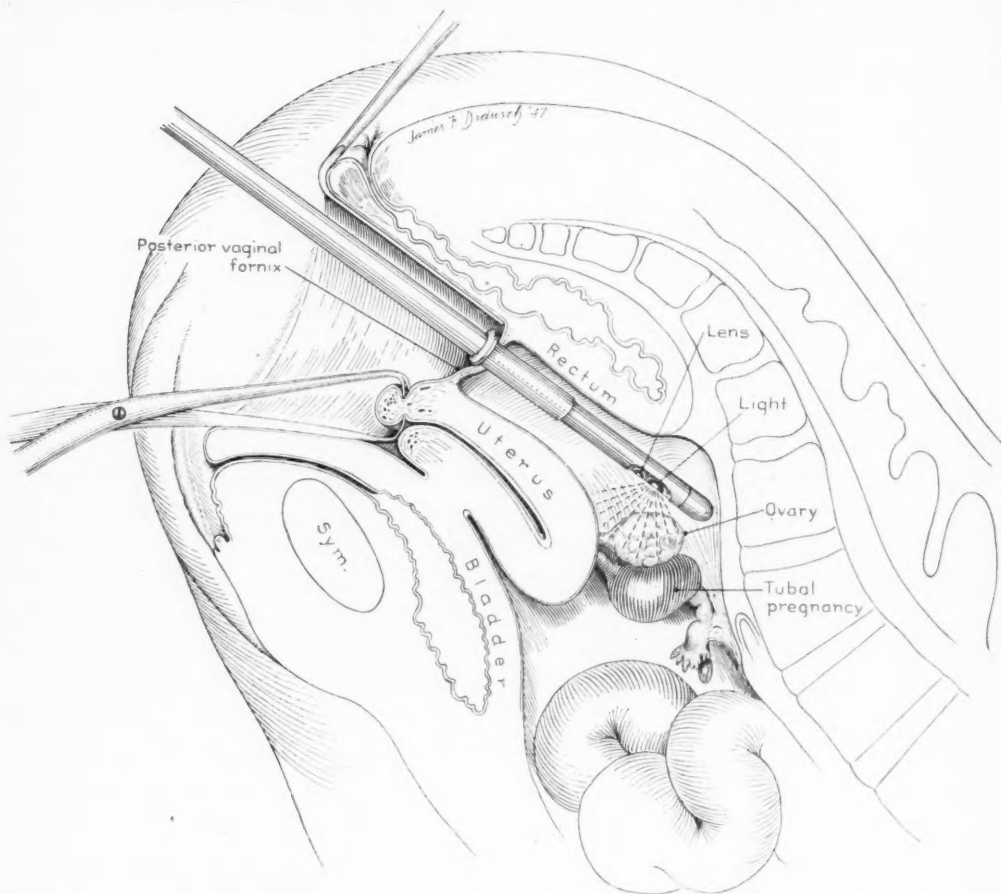


Fig. 2.—Sagittal view showing the patient in the knee-chest posture and culdoscope in place. Note how the intestines fall away from the pelvic viscera.

The vagina is cleaned up as for a vaginal plastic operation. If the patient is unanesthetized, care must be taken to use a nonirritating antiseptic solution.

We have done the culdoscopic examination on many patients under local anesthesia by simply injecting several c.c. of 0.5 per cent nupercaine solution in the posterior vaginal fornix at the site of puncture of the trochar. When gen-

eral anesthetic is used, we have chosen intravenous pentothal sodium in 2½ per cent solution. It is usually given through a vein in the dorsum of the hand or wrist after the patient has assumed the knee-chest posture. We have chosen general anesthesia for those patients who appear to be rather nervous, and for those upon whom we have felt that immediate laparotomy was likely. All of our patients have been hospitalized for at least twenty-four hours.

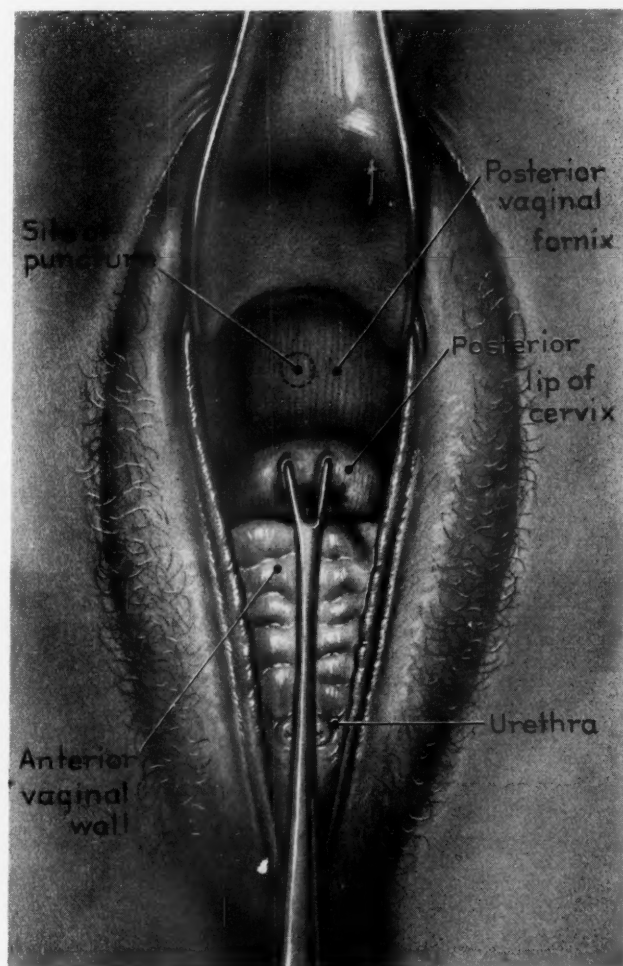


Fig. 3.—View of ballooned-out vagina with patient in knee-chest posture, showing site of puncture.

With the patient in the knee-chest position, the perineum is elevated with a Sims or other posterior vaginal retractor (Fig. 2). This permits air to enter the vagina and it balloons out, putting the mucosa of the posterior vault on considerable stretch. The spot at which the puncture is made is shown in Fig. 3. The novice is likely to puncture too close to the cervix, being afraid of injuring the rectum. If this mistake is made, the tip of the trochar ends in the retrocervical areolar tissue, and the cul-de-sac is not entered. If the puncture is made in the proper spot the stretched vaginal mucosa and peritoneum are easily perforated with a sudden quick puncture. As soon as the obturator is withdrawn there will be an audible in-rush of air if the tip of the cannula is in the cul-de-sac. If this

does not occur, it is obvious that it is not in the peritoneal cavity and that there is some adherent structure in the cul-de-sac. The latter possibility can usually be avoided by a previous careful bimanual examination.

The sterile culdoscope is then introduced through the cannula. It is to be noted that the culdoscope which comes in contact with the viscera never touches the vaginal mucosa, thus reducing the possibility of infection to nil.

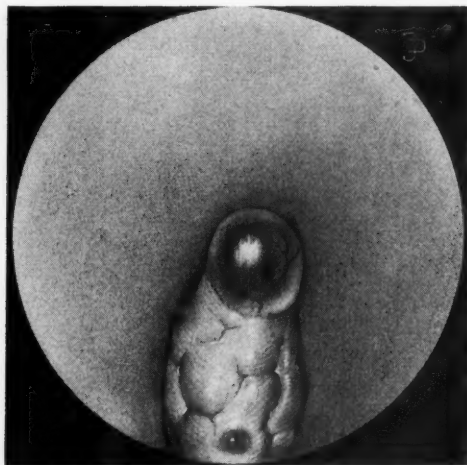


Fig. 4.—Culdoscopic view of normal ovary with corpus luteum.

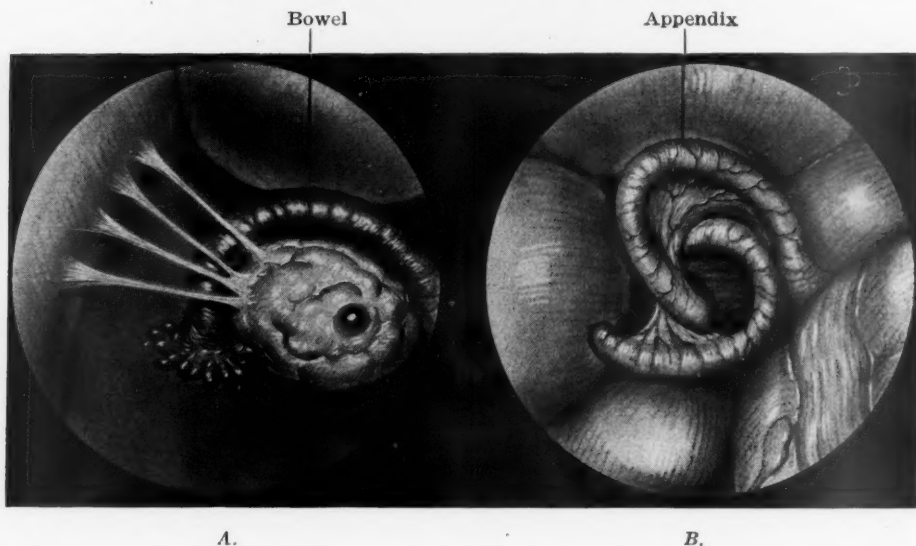


Fig. 5.—A. Culdoscopic view of ovary and tube. B. Culdoscopic view of appendix.

The uterus, tubes, ovaries, broad ligaments, uterosacral ligaments, infundibulopelvic ligaments, rectal wall, sigmoid, small intestines, and often the cecum, appendix, and even the ureters can be visualized. The culdoscope may be moved from side to side and rotated as necessary. The direction of visibility through the lens is indicated by a marker on the eyepiece. The viscera can be moved so as to come into view by manipulation with the tip of the culdoscope, by movement of the volsellum on the cervix or, better still, by

making manual pressure at various points in the suprapubic region. Occasionally, if the lens is introduced cold, it may become hazy, due to the body heat. Therefore, it is well to dip it in warm water and then wipe dry just before inserting it into the cannula. The lens magnifies structures to some degree, depending upon the distance it is from the object. As the tip of the culdoscope is drawn away from the object, a larger field is visualized and the individual structures seem smaller. Figs. 4, 5, and 6 are actual drawings by the artist of culdoscopic views of normal or nearly normal viscera.

If the object of the culdосcopy is to inspect the tubes carefully to determine points of obstruction, a self-retaining screw tip cervical cannula is introduced in the cervical canal. This is attached by means of rubber tubing to a syringe filled with a weak solution of methylene blue. As the fluid is forced in, distention of the tube can be seen proximal to the point of obstruction. If the tubes are patent, methylene blue can be seen dripping from the fimbriated ends.

On completion of the examination the culdосcope is withdrawn, but the cannula is left in place as the patient assumes the lateral recumbent position. Pressure is made by an assistant on the abdomen until the air is exhausted from the abdominal cavity. The out-rushing of air is quite audible. The wound in the cul-de-sac is not sutured. Fig. 7 shows wound in the cul-de-sac from within the abdomen two days after culdосcopic examination.

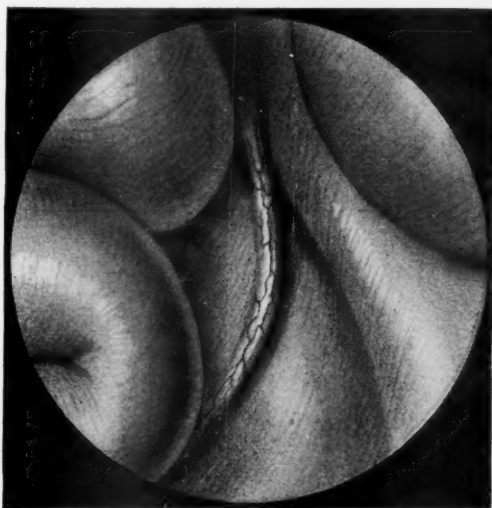


Fig. 6.—View of ureter which can occasionally be visualized.

Discussion

The greatest indication which we have found for culdосcopy is to gain more information in cases in which the history and/or pelvic examination suggest tubal pregnancy. Of the fifty-six cases of culdосcopy reported here, 37 were done for this purpose. Ectopic gestation is more often overlooked and more often diagnosed when not present than any other serious pelvic lesion. I doubt whether there is a gynecologist or obstetrician who has not made such errors. A correct diagnosis is imperative. Fearing the consequences of failure to diagnose an existing tubal pregnancy, many abdomens are explored, only to find no abnormality or a minor lesion for which surgery is not neces-

sary. In the typical case the diagnosis is simple, but a large percentage of tubal pregnancies are far from typical as to history and pelvic findings. On our Negro service we see great numbers of women who prove to have salpingitis, but the history and pelvic findings are so suggestive of ectopic gestation that we cannot dismiss them with a clear conscience. Of the thirty-seven patients who were culdoscoped because the history and/or pelvic findings were suggestive of tubal gestation, a diagnosis of tubal pregnancy was made in five instances.

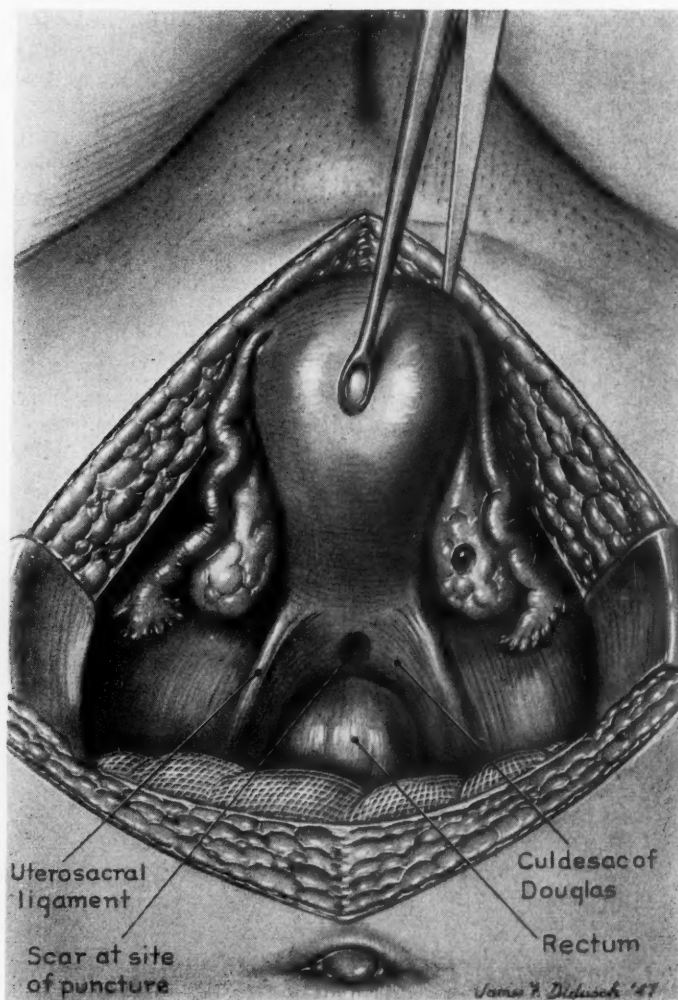


Fig. 7.—View of cul-de-sac wound two days after culdoscopy.

In each instance operation proved the culdoscopic examination to be correct. None of the thirty-two cases in which tubal pregnancy was excluded was found to have it by subsequent operation or observation. We do not mean to infer that in all of the thirty-two cases laparotomy would have been necessary to exclude tubal pregnancy with certainty. In some instances simple observation in the hospital would have eventually ruled it out; in others a pregnancy test,

curettage, or colpotomy would have led us to the right diagnosis. However, as a result of culdoscopy we were able to discharge many of these patients from the wards promptly and with safety, thus releasing much needed hospital beds.

It is only fair to say that in many instances simple colpotomy would have made or ruled out the diagnosis of tubal pregnancy with reasonable certainty. However, it is on occasion quite impossible to detect definitely an unruptured tubal pregnancy or even an early tubal abortion by colpotomy. On two occasions in the past simple colpotomy mislead one of us (R. W. T.) to interpret a small amount of blood in the cul-de-sac as indicating tubal pregnancy, when the bleeding actually arose from a corpus luteum and undoubtedly would have subsided spontaneously without serious effect. With culdoscopy such a satisfactory view of the tube and ovary is obtained in most instances that the exact origin of the bleeding can be detected and a correct decision for or against laparotomy made.

Salpingitis in some form was found to be the condition simulating tubal gestation in eighteen of the thirty-seven cases. There were three cases of retained placental tissue and one early intrauterine pregnancy. Three follicular retention cysts and one large corpus luteum were found. There was one case of endometriosis, and in five cases we were forced to make a diagnosis of unexplained abdominal pain. Subsequent operation or observation of these cases substantiated culdoscopic observations.

Other circumstances under which culdoscopy is useful are numerous.

Lower abdominal pain which is atypical in character and which is not satisfactorily explained by the usual gynecologic or other physical examination is one of the common problems which confronts every gynecologist. Often the conscientious gynecologist decides with the greatest difficulty whether a given patient warrants an exploratory laparotomy or whether she should be placed in the psychosomatic class. Mistakes are not infrequent in both directions. Many a psychoneurotic woman is subjected to an unnecessary exploratory laparotomy, and often a patient with real but undetectable pathology is classified as neurotic. In this series of patients there is one who had been examined by two excellent gynecologists only to be told that there was no organic basis for her complaint of left lower quadrant pain. One of us (R. W. T.) examined her and found her pelvis quite normal to palpation. Her complaint was so definite that we were loath to put her in the psychosomatic group. Finally, we culdoscoped her and found the left ovary adherent to the sigmoid by an endometriosis process. On bimanual examination the normal sized ovary moved perfectly freely with the sigmoid and was thought to be free of disease. Removal of the left ovary completely relieved the left lower quadrant pain.

In cases of severe dysmenorrhea there always exists the possibility of very early endometriosis, undetectable by bimanual palpation. Visualization of the ovaries and pelvic peritoneum may make a diagnosis and thus permit early conservative surgical treatment.

The differential diagnosis between salpingitis and endometriosis may, at times, offer considerable difficulty. To make such a differentiation may be of great value, for our attitude toward surgery in the two conditions is quite different. In young women the desirability of the preservation of the childbearing function is the aim in both conditions. This is best accomplished in most instances by nonoperative treatment when dealing with salpingitis. With endometriosis, on the other hand, early conservative surgery may permit future pregnancy, while delay in surgery may make conservative surgery impossible. The culdoscopic pictures in both conditions are quite characteristic, and the differentiation is easily made unless the cul-de-sac is obliterated by adhesions.

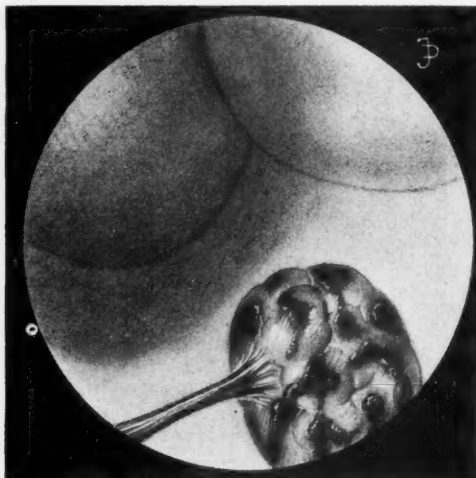


Fig. 8.—Culdoscopic wound of ovary with small blood clots in case of ruptured tubal pregnancy. The dark area in the background is old blood out of focus.

The differentiation between very early acute salpingitis and acute appendicitis is not always a simple matter. To carry out the proper treatment such a differentiation is essential without too much delay. A mistake in judgment may result in an unnecessary operation or rupture of the appendix. Although acute inflammatory conditions within the abdomen contraindicate peritoneoscopy, culdосcopy can be quite harmlessly done. In the very early stage of acute salpingitis there are few adhesions, and the tubes are easily visualized. Not infrequently the appendix can also be seen, but in any event enough information can be obtained in each instance to make the diagnosis with certainty.

Although we have not used culdосcopy for that purpose in this series of cases, we can conceive of circumstances under which it would be very advantageous in differentiating between Neisserian and tuberculous salpingitis.

Ovarian enlargement of lesser degree may give the gynecologist the greatest concern. To remove a follicular cyst which would probably ultimately disappear spontaneously is to perform unnecessary surgery. To permit a small neoplastic cyst to remain in the pelvis may have ultimate serious consequences. Watchful waiting is justifiable for a time, and the spontaneous disappearance of the cyst

settles the question quite satisfactorily. There are some cases, however, in which the ovarian enlargement persists even when it is not due to neoplasm. Usually the differentiation between a retention cyst or cystic ovary and a neoplasm is easily made through the culdoscope.

Not infrequently, in our experience, postmenopausal bleeding is not satisfactorily explained on examination of curettings. It is disturbing to have the bleeding recur in some of these women, and there remains the possibility of an early nonpalpable ovarian or tubal neoplasm. This can be determined with greater assurance by culdoscopy.

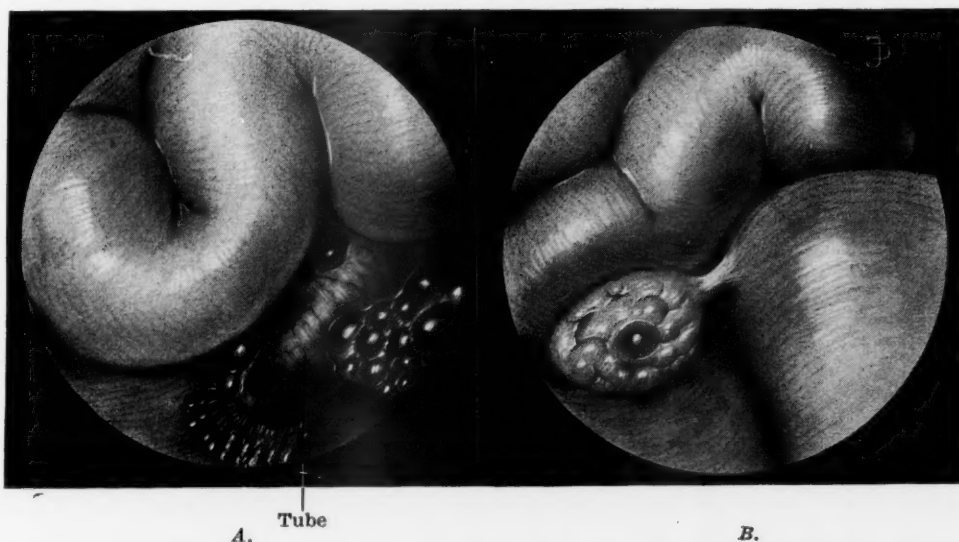


Fig. 9.—A. Tubal pregnancy with tubal abortion. B. Normal ovary on opposite side. The tube on this side was previously removed because of a tubal pregnancy.

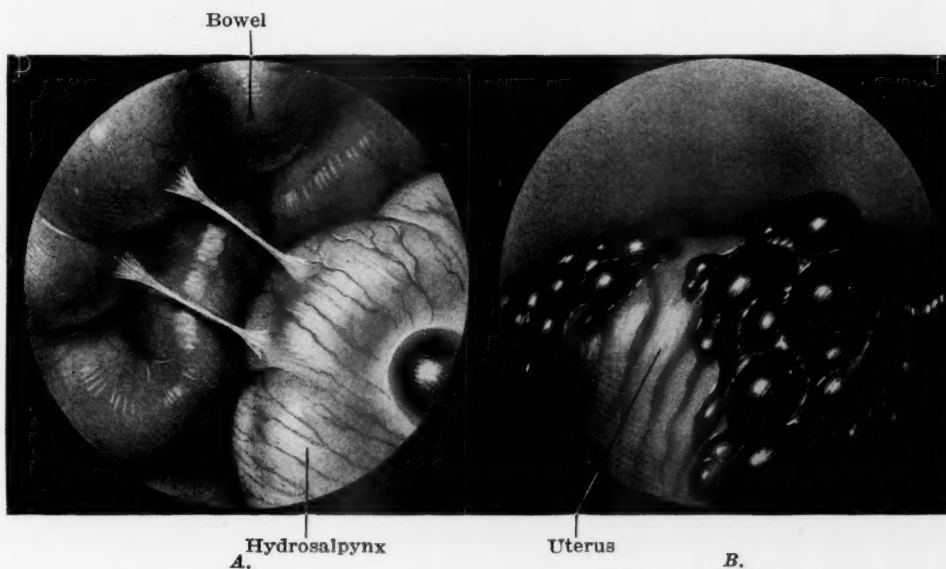


Fig. 10.—A. Culdoscope view of hydrosalpinx. B. Blood clot on posterior surface of uterus in case of ruptured tubal pregnancy.

In certain endocrine disturbances, such as functional bleeding, functional amenorrhea, ovarian dwarfism, and ovarian agenesis, exact knowledge of the anatomic and, to some degree, the physiologic condition of the ovaries can be learned only by culdoscopy or exploratory laparotomy. The advantages of culdoscopy are apparent. The knowledge thus gained may prove of value in therapy, and subsequent culdoscopic examinations may prove valuable as a check on therapy.

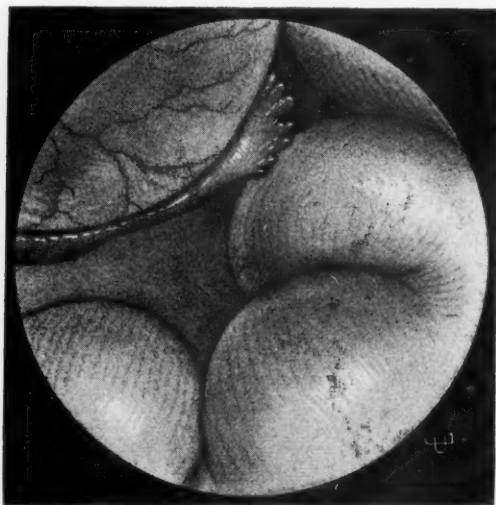


Fig. 11.—Culdoscopic view showing portion of an ovarian cyst with tube stretched over it.

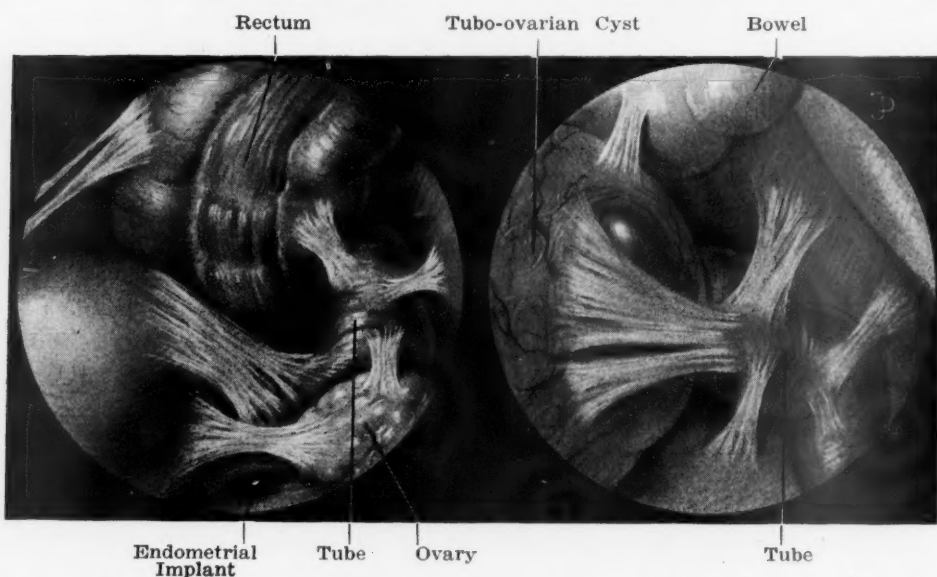


Fig. 12.—Culdoscopic views of adnexa in case of residue of endometriosis and of pelvic inflammatory disease.

Finally, the culdoscope is of value in investigating sterility. Just how valuable it will prove to be will become apparent as we extend our experience with it. Much information can be gained about the condition of closed tubes

and the likelihood of opening them by plastic surgery. Also the role of the ovary in sterility can be evaluated by observing follicles and corpora lutea as well as the presence and character of peri-ovarian adhesions. Our present attitude is one of conservatism in its use in sterility cases, but, at any rate, it is one more method available to us of gaining fairly accurate data in selected cases of infertility.

Figs. 8 to 12 show culdoscopic views of various lesions which we have encountered.



Fig. 13.—Shows flat plate of abdomen in a patient with retroperitoneal emphysema.

Contraindications, Failures, and Accidents.—The chief contraindication which we have found to culdoscopy is the presence of a fixed mass in the cul-de-sac. Occasionally a much contracted senile vagina will not permit a satisfactory puncture of the posterior vaginal vault. Also vaginitis contraindicates the entering of the cul-de-sac. A very ill patient, especially one with cardiac decompensation, had best not be put in the knee-chest position but the indication for culdoscopy in such a case would be extremely rare.

Culdoscopy was totally unsatisfactory in two of the fifty-six cases of this series because of a fixed mass in the cul-de-sac. In the light of our present experience no attempt would be made to culdoscope a patient with such a condition. In one other case it was totally unsatisfactory because of cul-de-sac ad-

hesions. In only a few other cases was it only partially successful because of adnexal adhesions.

In one of the two unsuccessful cases in which the uterus was adherent in the cul-de-sac a peculiar accident occurred. Apparently the trochar passed no further than the subperitoneal space. Air spontaneously entered this space and apparently was trapped there. The next day subcutaneous emphysema was noted over the upper trunk. This persisted to some degree for four days. No harm resulted, and the patient was not uncomfortable. Fig. 13 shows a flat x-ray plate of the abdomen with retroperitoneal emphysema. In two other cases we neglected to force the air out of the abdomen and the patients were moderately uncomfortable for a few days. Fluoroscopy and x-ray plates showed considerable air in the upper abdomen (Fig. 14).

We have had no instances of hemorrhage, peritonitis, or injury to a viscus. Decker reports one case of injury to the rectum with the trochar. The rectal opening was not closed, and the patient recovered without temperature elevation or discomfort.

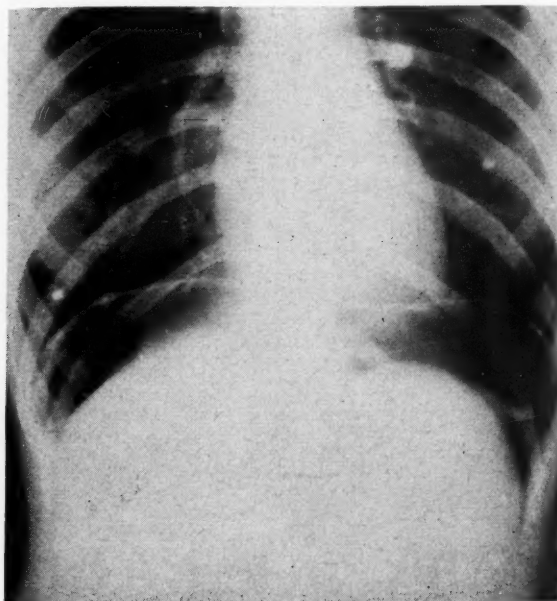


Fig. 14.—Note subdiaphragmatic collection of air twenty-four hours after culdoscopy and failure to force out air from the peritoneal cavity.

Conclusions

Our experience in this series of fifty-six cases in which culdoscopic examination was done brings us to the conclusion that it is a valuable adjunct to the more usual gynecologic procedures. Our prediction is that it will be used eventually with increasing frequency in most clinics. I am reminded of the words of the late Rubin Peterson when in the early days of radiograph studies of the pelvic organs he said, "After some thirty years of experience, I took it for granted that there was very little to be felt in the pelvis that I could not

feel. Now, however, I must confess that after my experience with pelvic roentgenology, my eyes have been opened to the fact that there are possibilities in relation to preoperative diagnosis that I never dreamed of." A statement such as that would seem to be justified regarding the direct visualization of the pelvic organs by culdoscopy.

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Discussion

DR. JOHN ROCK, Brookline, Mass.—I have applied this method in 87 patients. I have not been as deft nor as accurate as Dr. TeLinde, because I have failed to enter the cul-de-sac in fifteen cases, that is, one in six. I found that many of the early failures were due to the fact that the point of the obturator had become bent, it merely pushing the peritoneum ahead of it and the alveolar space was entered.

I also made the mistake at first of attempting to enter the cul-de-sac a little too near the cervix. In one patient I am pretty sure that there was just too much fat between the peritoneum and the epithelium, and I attempted to use local anesthesia. I did not realize that the epithelium is so closely approximated to the peritoneum, and that one cannot infiltrate the pelvic cavity.

If the patient does not require general anesthesia, I try to divert her mind and do not use even local anesthesia. Strangely enough, there is comparatively little pain to it. I used carbon dioxide for the first thirty or forty cases. I used pressure to put it in, and that sometimes infiltrates the tissue with gas. I have found now that the use of air is satisfactory, and, with care, pressing on the abdomen and the flanks, the air can be pressed out and the patient made comfortable. The patients have gone home usually on the same day of the examination. Of those who went home promptly, only two or three complained of real distress. Many had shoulder pains such as after insufflation.

I did suture several of the early patients. Most of my cases were sterility patients in whom I could not find any explanation for the sterility. All methods of examination seemed to indicate normality, and yet there had been three or four years of mating. I suspected something to be wrong in the pelvis. I found adhesions involving the right tube fifteen times, the left tube fifteen times, and adhesions of the ovaries three times. These findings were confirmed at subsequent examination in 27 of 28 cases. I examined one patient who gave a history suggestive of ectopic pregnancy and found a large cyst of the ovary. At examination one patient was found to have a solid tumor lying close to the uterus on the left side. She was in the menopause and did not want an operation.

Culdoscopy is a very useful bit of technique in surgery and, as far as I can tell, is comparatively harmless.

DR. JOSEPH L. BAER, Chicago, Ill.—At Michael Reese Hospital, we have concentrated on pelvic roentgenography for over one-fourth of a century. I venture to say that the collection of slides which has been accumulated by Dr. Irving Stein, of our hospital, is perhaps the very best collection of pictures of the pelvic viscera, obtained either by transuterine or trans-abdominal methods, which is extant in this country. We have found this method useful in confirming diagnoses. I believe this method proposed by Dr. TeLinde is one that should be investigated by anyone who is using pelvic roentgenography.

From the literature and from my colleagues I have the impression that direct study of the pelvic viscera, either by roentgenograph or any other method except open surgery, is sadly neglected, and so I speak on behalf not only of Dr. TeLinde's addition but also on behalf of pelvic roentgenography, either transuterine or transabdominal—a device which definitely adds something to our diagnostic acumen.

DR. TELINDE (Closing).—I believe there are two reasons why Dr. Decker's culdoscope has not been generally accepted. One is that we are all lazy and it is so easy to make a midline incision and see what is in the pelvis; it is a little more difficult to get the patient in the knee-chest position and make the diagnosis by culdoscopy. Another reason is the fear of puncturing a viscus. We have never punctured a viscus. Decker punctured the rectum on one occasion. He simply withdrew the trochar and the patient had no elevation of temperature or other disturbance.

REACTIONS OF THE VULVA TO SYSTEMIC DISEASES*

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UNCERTAINTY surrounding the etiology and management of a number of nonvenereal lesions affecting the vulva caused the present study to be initiated. As investigation progressed it became more apparent that the skin of the vulva represents an area of body surface which readily responds to many internal diseases. Since the gynecologist is often consulted concerning lesions of this area, an understanding of reactions of the vulva to systemic diseases is of real clinical importance.

Through the writings of such authors as Jones¹ and Taussig,² the external genitals of the female have come to be known as the vulva, meaning those structures external to the hymenal ring. Through common usage vulval anatomy now includes the vestibule, urinary meatus, clitoris, labia minora, mons veneris, labia majora, Bartholin's glands, and the perineum.

The vulva develops from outgrowths of mesenchyme covered with ectoderm.³ These ectodermal tissues have characteristic features. The labia minora and clitoris are normally covered with a soft, pliable, stratified epithelium containing sebaceous glands, but no hair follicles and few, if any, sweat glands. The skin of the mons veneris, labia majora, and perineum characteristically has a well-developed horny epithelium, a profusion of hair follicles, sebaceous glands, and many large and small coil sweat glands.⁴ Like other excretory skin structures, the compound racemose Bartholin glands with their columnar epithelium, fibrous capsule, and thin, clear, alkaline secretion are subject to systemic stimuli.

The corium or dermis of the vulva is made up of collagenic connective and elastic tissue of varying thickness containing an abundance of nerve fibers, blood and lymph vessels, hair follicles, and glands. The cutaneous vessels supply the skin with products for regeneration, nutrition, and growth. They carry away many of the products of skin metabolism. A dense network of small blood vessels spreads out as a very complete sheet in the most superficial part of the corium parallel to the outer skin surface. These minute terminal arterioles and capillary loops represent the major area of metabolic exchange in the skin.⁵

Since the epithelium contains no blood vessels, its nourishment is received through lymphatic exchange in the intracellular spaces. Pathologic manifestations from systemic diseases are usually first seen in the underlying corium where the capillary loops are in contact with the basal cell layer of the epithelium. Skin changes from internal disease occur from within outward.

*Presented, by invitation, at the Seventieth Annual Meeting of the American Gynecological Society, the Seigniori Club, Montebello, Quebec, June 17 to 19, 1947.

General Considerations

From a clinical point of view it is important to consider the abundant network of nerve endings in the papillae of the dermis. Meissner's corpuscles, end bulbs, and genital corpuscles are plentiful beneath the skin of the labia minora and clitoris. Pressure receptors, the Paccinian corpuscles, are found in abundance in the connective tissue structures of the labia majora and clitoris. The small capillary loops supplying the skin occupy an area in the papillae of the corium in close proximity to nerve endings. It seems reasonable that any internal condition which gives rise to destruction of, or edema around, the small blood vessels would cause considerable irritation of the nerve endings.



Fig. 1.—Edema of the vulva associated with severe toxemia of pregnancy. Asymmetric enlargement of labia was due to a straddle injury in which the vulva struck the side of a bathtub. Vulval edema did not interfere with the spontaneous birth of an infant weighing 2,700 Gm.

In the human subject there are no cyclic changes in the epithelium of the vulva similar to those found in structures of Müllerian duct origin. With regard to changes of the external genital structures associated with puberty, pregnancy, and the climacteric period, there is no variation in the response of the skin of the vulva from that covering other surface areas of the body. The areolae and surrounding skin of the breasts react to endocrine influences in a manner quite parallel to the vulva. While these endocrine influences do cause changes in the secretory appendages of the epidermis, the greatest amount of hypertrophy, and therefore involution, associated with growth and regression is in the underlying

tissues which are of mesodermal origin. Considering the epidermis of the vulva as tissue quite comparable to other surface coverings of the body such as the breasts and lips, it seems probable that the subepithelial structures and the location of this area in relation to the organs of excretion are more important than the inherent characteristics of the epithelium itself.

Frequent trauma, constant contamination, warmth, and moisture increase the metabolic demands of the surface epithelium of the vulva. Where these conditions prevail, skin resistance to systemic disease is decreased.

The large amount of subcutaneous areolar tissue, the folds of easily distended epithelium, and the large number of blood and lymph vessels permit tremendous edema of this area. Edema frequently accompanies and probably contributes a great deal to the itching associated with such conditions as toxemia of pregnancy, urticaria, herpes zoster, the early forms of atrophic dermatitis, and many other skin conditions which involve the vulva.



Fig. 2.—Psoriasis of the vulva, thighs, and perianal area. Lesions on the vulva were distorted by irregular lichenification and ulceration.

In trying to arrive at a diagnosis of a noninfectious vulval lesion, there are a few important points in history taking which may be outlined as follows: (1) The duration of the condition. (2) The character of symptoms, particularly with reference to the degree of itching and edema. (3) The exact site of origin of the complaint (this frequently is best obtained by having the patient point directly to the area of initial involvement). (4) History of dermatologic reactions to common substances such as soaps, ointments, medications, disinfectants, douching materials, and clothing. (5) History of menstrual function. (6) Diurnal variation of symptoms. External irritants are usually noticed during the day. Epithelial irritations of internal origin often become more intense at night.

Dermatologic lesions always warrant careful evaluation. At the turn of this century Fox expressed an opinion regarding dermatology which is particularly applicable to diseases of the vulval epithelium. He stated that a name alone for a pathologic condition is not enough, but that an accurate appreciation of the conditions which are present both in the skin and in the internal organs, as well as the various causes which tend to produce these conditions, should be determined in each instance.⁶

At examination it is well to remember that common skin lesions such as lichen planus, allergic reactions, herpetiform infections, psoriasis, and other dermatologic conditions which cause changes in the epithelium may be greatly distorted in the vulva due to secondary infection and ulceration. In every patient with vulval disease the gynecologist should not only inspect the vulva but look elsewhere for skin lesions. The lips, mouth, tongue, hair line, axillae, palms of the hands, back, and breasts are particularly important areas for investigation. Signs of infections should be looked for in the urethra, Bartholin glands, vagina, and cervix.



Fig. 3.—Ulceration of the vulva in aplastic anemia.

In all instances of vulval ulceration, minimal laboratory studies should include a complete blood count; urine examination, particularly for sugar and acetone; cultures for gonococci and mycotic organisms; and a hanging drop examination for *Trichomonas vaginalis*. Indications for biopsy, venereal disease tests, and special blood chemistry studies should be determined by the history and characteristics of the lesion.

Blood Dyscrasia

Agranulocytosis, aplastic anemia, and acute leucemia cause peripheral vascular changes which result in deep, punched-out, oval areas of vulval ulceration

covered with a thin, grayish membrane and surrounded by very little induration or redness. An example of this type of ulceration in a patient with aplastic anemia secondary to sulfanilamide poisoning is given in Fig. 3.

This patient had received approximately 15 Gm. of sulfanilamide from her family physician for treatment of a sore throat. When admitted to the hospital, two weeks after receiving the sulfanilamide, she was found to have ulcerative lesions of the oropharynx similar to those found on the vulva and in the vagina, as well as retinal hemorrhages and bleeding from the gum margins. Her hemoglobin was 35 per cent; red blood count was 1,280,000, and the white blood count was 1,040, with 96 per cent lymphocytes and 4 per cent neutrophils. Prior to death her white blood count went down to 770 per cubic millimeter, all of the cells being monocytes. Bleeding time was twelve and one-half minutes. Prothrombin time was 57 per cent of normal. Blood platelet count varied from 48,000 to 27,300 per cubic millimeter.



Fig. 4.—Ulceration and hyperpigmentation of the vulva in pernicious anemia.

Pernicious anemia is a deficiency disease which gives rise to tissue devitalization. The sensitive epithelium of the vulva readily reflects the avitaminosis and disturbed metabolism associated with pernicious anemia. Vulval lesions in a patient with an acute exacerbation of pernicious anemia are shown in Fig. 4. This patient's hemoglobin was 20 per cent; red blood count was 670,000, and the white blood count was 2,050. Gastric analysis showed no free hydrochloric acid. Blood urea nitrogen was 19 mg. per cent. Areas of ulceration with secondary surface infection were found in the bladder mucosa, tongue, and mouth, as well as on the vulva. With treatment consisting of blood transfusions, liver extract, thiamin chloride, nicotinic acid, and cevitic acid, all of the surface ulcers promptly healed.

The Vulva in Uremia

A typical ulceration of the vulval epithelium occurs in patients with slowly developing uremia. In gynecology, uremia is most frequently seen complicating carcinoma of the cervix. Weight loss, tissue dehydration, and avitaminosis contribute to the typical vulva changes seen in uremia. The inner surfaces of the labia minora and the most dependent parts of the labia majora show a superficial excoriative type of ulceration, covered with a thin, grayish membrane and surrounded by brownish encrusted crystals of urea and uric acid. In the case of a patient with carcinoma of the cervix and bilateral pyelonephritis, the blood urea nitrogen was 75 mg. per cent. Following treatment of her pyelonephritis and avitaminosis, the blood urea nitrogen returned to 15 mg. per cent and the vulva healed.

Diabetes Mellitus

There are several factors in diabetes mellitus which produce circumstances favoring dermatitis of the vulva. Inadequate metabolism of carbohydrates and fats causes disturbances in cellular nutrition. Diabetic patients on a high carbohydrate diet and large doses of insulin frequently show symptoms of B avitaminosis. Great utilization of carbohydrate rapidly exhausts any scant supply of nicotinic acid and riboflavin which the patient may have.⁷ Vitamin deficiency causes edema and itching which results in trauma to the epithelial surfaces of the vulva. Another way in which the diabetic patient develops vulvitis is due, in all probability, to the glucose-containing urine keeping the vulva moist. This is particularly true of the patient with constant dribbling. The sugar-containing urine and sebaceous secretions present on the vulva result in a culture media quite favorable for the growth of fungi and many other bacteria common to this area. Quite frequently intertrigo from obesity contributes to the diabetic patient's vulval dermatitis (Fig. 5).

Treatment of the diabetic patient with vulval infection should be directed first to correction of the diabetes plus adequate supplemental vitamins, particularly those of the B-complex group, and reasonable cleanliness. Various local applications may be used to combat surface infections, depending upon the etiology of the predominating organism. In mycotic vulvovaginitis, good results have been reported with treatment consisting of a nonirritating, nonstaining jelly containing calcium and sodium propionate.⁸ The important principle is not to add an irritating therapeutic agent which will contribute additional trauma to the partially devitalized cutaneous structures. As soon as the systemic condition is corrected, the surface epithelium usually heals quite rapidly.

Vitamin Deficiencies

Probably the most common vitamin deficiency influencing the skin of the vulva is that associated with the B factors. Because the underlying vitamin deficiency is often mild and manifestations in the vulva are soon camouflaged by secondary infections, the basic diagnosis of vitamin B deficiency is frequently missed. A lack of riboflavin favors *Candida* (Monilia) infections. Skin ulcerations secondary to pellagra are often infected with Vincent's organisms.⁹ When

either of these infections is found in patients with pregnancy, diabetes, alcoholism, hyperthyroidism, fever, or any debilitating condition, vitamin B deficiency must be considered as a predisposing factor in the infection.

Vitamin B factors are essential in the continuous process of cellular nutrition and respiration. Sydenstricker indicates that thiamine, nicotinic acid, and riboflavin function partly as activators in carbohydrate dehydrogenation and are constantly regenerated. They also are components of coenzymes which are used up and require constant replacement. Disturbance in cellular function is due to the coenzyme action of these vitamins. Neurons are the cells most sensitive to the oxygen want association with early nutritional deficiency.⁷ This may be a factor in hypersensitivity and itching of the vulva before edema and changes in the epidermis are evident.



Fig. 5.—Dermatitis in a diabetic patient with urinary incontinence and intertrigo.

Bean, Spies, and Vilter have demonstrated that asymmetric skin lesions can be produced in a susceptible pellagrin without exposure to sunlight by any mechanism which prevents a blood supply sufficient in amount to satisfy the local tissue demands. Where local anoxia and increased metabolism prevail as in scars, pressure, irritation, friction, or inflammation, local lesions may occur.¹⁰

Increased metabolism and unknown factors associated with pregnancy disturb the normal vitamin requirements. The pregnant and lactating patient needs three times the thiamin supply of the nonpregnant patient.¹¹

According to Ashworth and Sutton,¹² estrogens do not aid in the utilization of the vitamin B components. When given to patients with subclinical vitamin

B deficiency, they may cause the appearance of lesions characteristic of thiamin, nicotinic acid, and riboflavin deficiency. Metabolism of estrogens increases the demand for vitamin B.

Many years before there was much discussion about vitamin metabolism, Fox recognized that "all therapeutic agencies which equalize the circulation, strengthen the digestive functions, induce refreshing sleep, and improve nutrition of the body will be found to be powerful factors in the cure of cutaneous disease."⁶ In addition to the rather typical lesions of riboflavin and nicotinic acid deficiency, a number of other conditions which frequently involve the skin of the vulva have been attributed to various vitamin inadequacies. There has been a recent tendency to assign specific vitamins to certain skin diseases. For example, patients with eczema have been reported to respond to pyridoxine;¹³



Fig. 6.—Chronic atrophic dermatitis of the vulva.

psoriasis has been treated successfully with vitamin D;¹⁴ lichen planus has cleared up under treatment with vitamin B complex;^{15, 16} and of particular importance to the gynecologist have been studies indicating the possible influence of vitamin A deficiency in the development of chronic dermatitis of the vulva with kraurosis and leucoplakia.^{17, 18}

The clinical significance of achlorhydria, a finding rather common to women past 50 years of age, in relation to skin changes in the vulva is not very clearly understood. It is known that gastric achlorhydria prevents the extraction of vitamins from their natural sources in food.⁷ Patients with longstanding vitamin A deficiency frequently show gastric hypoacidity.¹⁹ Thiamin and nicotinic acid are essential to the normal function of the gastroenteric tract.²⁰ However, in evaluating gastric acidity, the many factors influencing gastric secretion such as emotional status, reverse peristalsis, and salivary secretions must be considered along with the nutritional state of the patient. Mitra and Varma found no significant correlation between gastric acidity and the orogenital syndrome of

vitamin deficiency.²¹ The administration of dilute hydrochloric acid in therapeutic doses fails to raise the free acidity in the stomach during digestion of a regular meal. The spectacular therapeutic results sometimes obtained with dilute hydrochloric acid administration remain unexplained. Most foodstuffs have a neutralizing influence on hydrochloric acid.²² Additional investigation is needed to clarify the relation of achlorhydria and vitamins in skin changes of the vulva.

Chronic Atrophic Dermatitis of the Vulva

The terms "chronic atrophic dermatitis of the vulva," "leucoplakic vulvitis," and "kraurosis vulvae" are used interchangeably to designate a clinical syndrome in which the tissues of the vulva undergo a low grade inflammatory reaction with associated atrophic and hypertrophic changes in the corium and epithelium. Detailed clinical and pathologic changes which characterize this disease have been described in excellent articles by Taussig,² Graves and Smith,²³ Counsellor,²⁴ Usher and Campbell,²⁵ Adair, Davis, and Schuitema,²⁶ Brewer,²⁷ and Savill.²⁸



Fig. 7.—Section of chronic atrophic dermatitis of the vulva showing marked hyperkeratosis, acanthosis, distortion of the basal cell layer, vascular dilatation, hyalinization of the dermis, and round cell infiltration.

A brief discussion of chronic atrophic dermatitis is included in this presentation to emphasize the internal factors which may contribute to its etiology. While the cause of this disease remains unknown, neurogenic, hormonal, nutritional deficiency, and allergic theories imply a subepithelial beginning for the atrophic and hypertrophic changes which characterize the condition.

Current studies seem to indicate that the primary histopathologic change in chronic atrophic dermatitis of the vulva involves the papillae of the corium and the basal cells of the epidermis (Fig. 7). This is the vital metabolic zone of the skin. Any disturbance in this zone will be reflected in the epithelium and in the underlying mesodermal tissues.

Characteristic changes in the epithelium involve all cell layers. Atrophic changes, ulceration, and hyperkeratosis are so frequently found in a relatively small section of the vulva that it is difficult to distinguish distinct epithelial phases of the disease (Fig. 8). In normal metabolism the basal cells are the only epithelial structures which can reproduce. In atrophic dermatitis, the basal cell layer is distorted and frequently shows more than a normal number of mitotic figures. Hydropic changes in the basal and prickle cells are a common finding (Fig. 9). These two cell layers represent that portion of the epithelium in which there is a circulation of lymph. The outer three layers of the epithelium contain no lymph supply. In association with hyperkeratosis, the granular layer next to the prickle cells contains many granules of eleidin. The cause of hyperkeratosis is unknown. Cellular anoxia and friction stand out as significant possible factors in the excessive keratinization seen in leucoplakic dermatitis. Increased deposition of eleidin and keratin in the skin of older people is not limited to the vulva. These changes are often seen on the backs of the hands, over the knees and elbows, and about the mouth. The anatomic characteristics of the vulva and its close relationship to the excretory orifices contribute to the severity of keratotic skin changes in this part of the body.

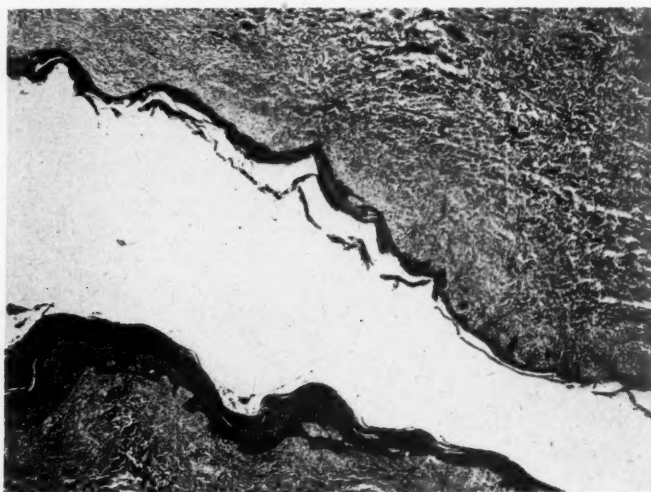


Fig. 8.—Atrophic dermatitis and hyperkeratosis in adjacent areas of the vulva.

Primary and secondary changes seem to occur in the dermis. Capillary dilatation and subepithelial edema disturb nerve endings, giving rise to itching. External trauma from scratching introduces bacteria into the subepithelial tissues. Healing of minute areas of ulceration is accompanied by the deposition of a homogeneous collagenous tissue which takes a connective tissue stain. Elastic fibers are reduced in number. Round cells infiltrate the dermis and extend into the germinal layers of the epithelium. Thus far, there is no clinical evidence that the collagenous scar tissue in the superficial portion of the dermis can be resolved by any type of therapy. This layer of avascular tissue deprives the

skin appendages of nutrition. Hair follicles, sebaceous glands, and sweat glands undergo atrophy. The epithelial surface may be edematous, glistening, red, wrinkled, retracted, white, or thickened, depending upon the degree of edema and scarring of the dermis, and upon the severity of surface infection secondary to external trauma.

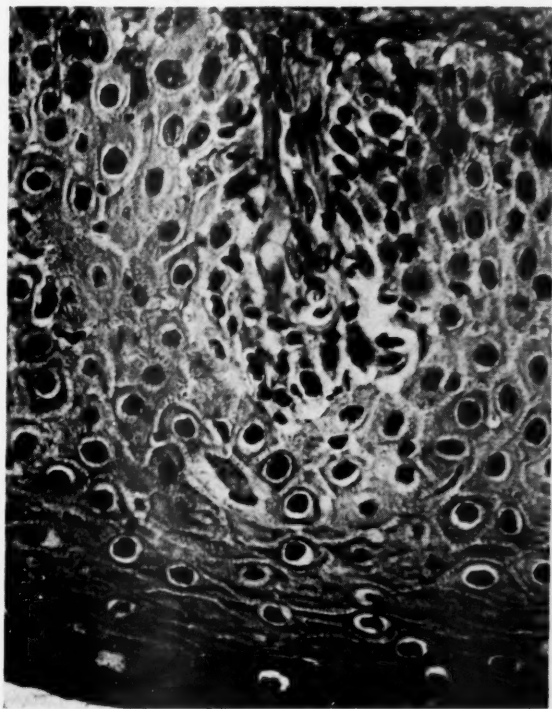


Fig. 9.—Section showing mitotic figures and hydropic degeneration of the basal and prickle cell layers in chronic atrophic dermatitis.

Treatment of atrophic dermatitis of the vulva has been directed at measures which reduce inflammation, alleviate pain, improve cell metabolism, and remove permanently damaged tissues. Eradication of all foci of infection is strongly advised. Nerve resection is recommended in selected circumstances.^{24, 25} At present, medical treatment with vitamins and estrogens frequently improves the skin condition of patients with atrophic changes of the vulva, but these forms of therapy should be used only in the early stages of the disease and under the most careful clinical control.^{17, 18, 29, 30, 31} Estrogen ointment applied locally produces as effective results in the epidermis of the vulva as oral administration of the drug. Local application carries with it none of the stimulating influences to the uterus and ovaries which are seen with the use of intramuscular or oral estrogens.

In the present state of our knowledge, where scarring causes symptomatic constriction of the vulva or where the vulva shows areas of ulceration and marked hyperkeratosis, the involved tissues should be removed by wide excision.

Allergic Dermatitis

Many women, particularly those of the older age group, show varying degrees of sensitivity to drugs, soaps, and clothing which come in contact with the skin of the vulva. It is difficult to say what part achlorhydria, deficient diets, and antibody formations have to do with these reactions. Frequently the skin of the vulva is not the only area showing localized sensitization. Some of the more common contributors to this type of localized dermatitis are: phenolphthalein, impure soaps, rectal ointments, phenol-containing douching materials, and underclothing. Poorly processed rayon and garments with incompletely fixed dyes are particularly common causes of vulvitis. Pure cotton or wood cellulose used in making rayon should cause no allergic reaction. However, synthetic resins, sulfonated oils, and formaldehyde preparations used to process or finish rayon may become important sensitizing agents which give rise to localized dermatitis.³²

As observed on the vulva, the first reaction to localized allergic dermatitis is edema and itching followed by secondary trauma from scratching. The labia become swollen. The sebaceous glands of the labia minora stand out in relief. There is puckering about the hair follicles of the labia majora as a result of subcutaneous edema. Fissures form over the perineal body and in the labial folds.

In arriving at a diagnosis, a careful history is essential. Because the patient has a localized sensitization to an unconcentrated irritant, patch tests are usually unsatisfactory. Two patients illustrate these points.

CASE 1.—One month following repair of a complete procidentia, a white patient 60 years of age returned for postoperative examination with a newly acquired extensive dermatitis of the vulva. Tense, shiny, thin epithelium covered the edematous labia. Lateral to the labia majora there was an increased amount of pigmentation. Linear fissures were present in the labial folds posteriorly. She had noticed a controllable amount of itching of the vulva. Her hands were healing from a slight rash which she thought resulted from the use of a cheap, highly scented soap. Examination showed no evidence of anemia, avitaminosis, or glycosuria. Stilbestrol ointment and a diet high in vitamin B failed to produce any remarkable improvement in the patient's vulval condition. On closer questioning it was found that her particular vulval reaction had come about while wearing certain newly acquired undergarments. As a clinical trial, all local treatment was stopped and the patient was asked to wear the rayon clothing in contact with the vulva day and night for one week. The intensity of the vulvitis increased immensely (Fig. 10). Thereafter, the only treatment advised was a change to cotton underclothing. Within a period of four weeks the vulva had healed completely. Three months later the patient gave herself another clinical trial with rayon. Her symptoms returned, but rapidly subsided as soon as the rayon no longer came in contact with the vulva.

CASE 2.—Another example of vulval sensitivity was that of a nurse, aged 53 years, who had had itching in the region of the labia and perineum for a period of six months. The itching became worse during the day and was especially noticeable by evening. She had been using an antiseptic powder containing carbolic acid in a douche. Her history included a marked reaction to some rayon and wool undershirts which had been packed in a moth preventative. She had been on a diet low in protein and roughage due to a gastrointestinal

condition which had been diagnosed as visceroptosis and spastic colitis. Medical examinations had shown achlorhydria. Significant findings were localized to areas where she had come in contact with synthetic materials. There was a linear ulceration behind her left ear immediately beneath the plastic material covering the framework of her glasses. Her external genitals showed oval, raised areas of superficial ulceration taking on an irregular pattern over the most prominent portions of the somewhat edematous labia and perineum. There was no inflammation around the anal orifice. The patient's vulval lesions and the ulceration behind her left ear cleared up within three weeks after the plastic guard was removed from her glasses and after she changed to a nonirritating type of undergarment.



Fig. 10.—Allergic dermatitis of the vulva resulting from sensitivity to rayon.

Summary

Regional reactions of the vulva to a number of noninfectious systemic diseases may be explained by anatomic and metabolic factors peculiar to this area of the body surface. Because of its vascularity, abundant nerve supply, frequent trauma, constant contamination, warmth, moisture, and variable histologic structure, the vulva frequently reflects deficiency diseases, metabolic disorders, and allergic reactions. The gynecologist is often consulted concerning lesions of this area which are, in reality, indications of internal disease. Some clinical points in identification of vulval lesions associated with such diseases as diabetes mellitus, pernicious anemia, aplastic anemia, uremia, vitamin deficiency,

chronic atrophic dermatitis, certain common dermatologic conditions, and allergic reactions have been described and illustrated with colored slides.

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Discussion

DR. JEAN PAUL PRATT, Detroit, Michigan.—Skin lesions of the vulva present interesting problems for diagnosis and treatment. Dr. Parks has selected a number of excellent characteristic illustrations. He has also presented a sound anatomic basis explaining the lesions.

I should like to describe a few cases to illustrate a group of metabolic disturbances which show evidence of hyperthyroidism and a lowered threshold for sugar.

The first is a girl 16 years of age who complained of itching and discharge. She was slightly overweight for her height and age, but generally healthy. We found this typical change of the skin of the vulva which shows a metabolic disturbance and, in addition, scratch lesions which became infected. The scratch lesions responded to antiseptic treatment promptly, but the skin lesion remaining was found to be largely due to hyperthyroidism. Her basal metabolism rate was minus 10, sugar tolerance normal. She tolerated 2 grains of thyroid, but her trouble was not relieved until carbohydrates in her diet were reduced. Control was difficult, as she was away from home at school most of

the year. Her intelligence permitted satisfactory management of her therapy by herself, particularly after the benefit to be derived from treatment was demonstrated to her. So long as she adheres strictly to the prescribed treatment she remains symptom-free and local evidence of metabolic disturbance disappears.

Another girl 10 years of age complained of itching. The change in the vulva which was also very suggestive of a metabolic disturbance was found. Her basal metabolic rate was minus 2; glucose tolerance was normal. She tolerated only one-fourth grain of thyroid. A low carbohydrate diet was advised. Treatment was carried out by her pediatrician, who informed us that more than one-fourth grain of thyroid produced symptoms of asthma. In a month she was improved but not relieved of itching. After eighteen months the character of the lesion had changed and was then typical of psoriasis, though she had not complained of any other lesion on the body and none were found. Here we were mistaken in our diagnosis. This patient's lesions looked like those of the first patient, but this proved to be a local psoriasis.

A third patient, a woman of about 55 years, complained of intensive itching and a vaginal discharge. The itching was the major problem, and the lesion suggested atrophic dermatitis. She had some evidence of metabolic disturbance and was treated with a low carbohydrate, high protein diet. She experienced some relief, but the lesion improved only up to a certain point. She remained so disturbed that she was only relieved by a vulvectomy.

A similar patient about 55 years of age was disturbed with itching. She was rather obese, had a normal basal metabolism, and a normal sugar tolerance. We have learned by experience, however, that the laboratory tests do not always make a correct diagnosis, and that therapeutic tests are often more valuable.

We reduced the carbohydrates in her diet. She tolerated about a grain of thyroid. This patient loved to eat and thought the treatment was hardly worth while and returned to her sweets. She returned feeling that the treatment was of very little use, but after three trials she was convinced that the cure lay within her own hands. As long as she continued the treatment we advised she remained symptom-free.

Another patient showed an atrophic vulvitis with ulceration. We saw her only once and found the symptoms rather characteristic of a metabolic disturbance in connection with the atrophic vulvitis. She was given thyroid to tolerance, a low carbohydrate diet, and stilbestrol. Her physician reported that she was entirely well six months later. We were suspicious that the ulcer might be malignant and we were relieved to learn that the ulcer had healed.

The patients just presented demonstrate the value of therapeutic tests when laboratory tests are negative. A normal basal metabolic rate and normal sugar tolerance do not exclude the possibility of metabolic changes in the skin of the vulva.

DR. FRED L. ADAIR, Chesterton, Indiana.—In discussing the excellent presentation, one is inclined to re-emphasize the fact that the obstetrician and gynecologist must never neglect to consider that he is dealing with an individual woman and not with an anatomic and physiologic set of organs or their parts: and that these structures are subject to disorders which may be of local origin or the local reaction be due to a more general condition which has a major local reaction.

There are some points of local interest which should be stressed. The vulva is the most complicated of the dermatologic structures of the human body with its hair follicles and sebaceous and sudoriparous glands; its various types of epithelia and modified glandular structures. It is also complicated with numerous folds and pockets which are in contrast to the more generally smooth dermal structures of the rest of the body.

One can also postulate that this area not only responds to the growth, development, age changes, and abnormal manifestations of other skin structure, but that it participates in the changes which occur in the sex organs at the onset of the menopause, also in those which occur as the result of pregnancy, parturition, and the puerperium. It is also worthy of note that no region of the human body is exposed to the effects of the discharges, normal and

abnormal, of so many and varied orifices. These discharges are modified not only by local disorders but also by diseases of remote organs and tissues. Their effect may be either direct or indirect.

We are confronted with a variety of local manifestations which are the result not only of regional factors, but may also arise from hereditary and environmental conditions independently or concomitantly with other dermatologic disorders.

Formerly, we at the University of Chicago did some work on a condition known by various names which we described as chronic atrophic dermatitis. We felt that fundamentally it was an atrophic condition of the dermis which affected the vessels, nerves, and tissues of the corium. It was our opinion then that, when the itching and irritation could not be relieved, excision was the best procedure not only to relieve symptoms but also to reduce the real threat of the development of carcinoma.

If the measures suggested by Dr. Parks or new means of alleviation arise in the future, the indications for removal might cease to exist.

In conclusion, I should like to stress again the ideas presented by the author that one should not be satisfied with a diagnosis of a local disease necessarily of local origin, but should evaluate all local and general factors which could be responsible for the regional manifestations. The diagnosis should be based upon the status of the patient and not be limited to the condition of the vulva.

DR. PARKS (Closing).—A point has been brought up which I should like to emphasize, and that is the use of stilbestrol in the treatment of vulval disease. For skin lesions, local application seems just as effective as systemic administration, and the patient experiences none of the uterine changes associated with its general use. In addition, stilbestrol seems to influence vitamin B metabolism. Skin lesions of patients with vitamin B deficiency may be aggravated by the use of stilbestrol.

A CLINICAL AND HISTOPATHOLOGIC STUDY OF LESIONS OF THE CERVIX UTERI DURING PREGNANCY*

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AN IMPORTANT feature of prenatal care is a careful inspection of the cervix uteri. This procedure often reveals pathologic lesions which exist with or without symptoms such as vaginal bleeding and demand immediate attention. The object of this study is to present an analysis of the histopathologic findings in a series of 89 cases where a gross abnormality was recognized, and a biopsy of the cervix obtained, or a hysterectomy performed.

Material

This study is based on the examination of tissue obtained from the cervix uteri of 89 patients at various stages of gestation. Pedunculated growths such as cervical and endometrial polypi had been removed by twisting off with a pair of forceps or a snare, and were available in toto for examination. The recognition grossly of carcinoma, condyloma, and leucoplakia called for a biopsy from the site of the lesion. In the group listed under "erosion of the cervix" the diagnosis in twenty-eight cases was based on biopsy specimens which had been obtained because the observer considered the appearance of the cervix as suspicious of a possible malignancy. In four instances a total hysterectomy had been performed because of a mistaken diagnosis, and all occurred before 1930, that is, before facilities for the routine performance of endocrine pregnancy tests had become available. The clinical description of these four cases mentioned the existence of a cervical erosion. Two cases, one with a cervical erosion and another with carcinoma, were ectopic gestations. Of the eighty-nine cases, forty were private patients under the care of various members of the staff, while forty-nine were from the clinic.

All stages of gestation are represented. Sixteen specimens were taken during the second month, twenty-six during the third, twelve during the fourth, seven during the fifth, twelve during the sixth, six during the seventh, six during the eighth, three during the ninth, and one at term. A survey of the age groups shows a fairly even distribution between 18 and 41 years, except for the cancer patients where the majority fell in the late thirties (Table II).

The histopathologic diagnosis showed the following distribution:

Cervical polypi	37
So-called erosion	32
Carcinoma	10
Condyloma acuminata	5
Endometrial polypi	3
Leucoplakia	2
Total	89

*Presented at the Seventieth Annual Meeting of the American Gynecological Society, June 17 to 19, 1947, Seignior Club, Montebello, Quebec.

The diagnoses of condyloma and leucoplakia scarcely need further comment. They were recognized grossly and were symptomless, except that bleeding occurred in one patient with condylomata, and in another there was a profuse leucorrhea. Both instances of leucoplakia merely showed whitish plaques on the cervix which histologically were composed of markedly thickened squamous epithelium. The basal cells showed no abnormal changes suggestive of a "pre-cancerous" or cancerous condition.

The Normal Cervix During Pregnancy

An enormous number of papers and monographs dealing with the gross and histologic changes in the cervix uteri during pregnancy has accumulated over a period of more than a century. For instance, in a monograph published in 1897, von Franqué¹ cited 210 references, and many articles have appeared since that time. These studies, however, have been concerned mostly with the formation of the lower uterine segment or with cervical dilatation during labor, and the generally accepted description of the cervix during gestation is that presented by Stieve² in his classic paper which appeared in 1927.

According to Stieve, there is during the premenstruum an enlargement and increased secretion of the cells of the cervical glands which he considered a preliminary to the transformation which occurs during gestation. In the first two and one-half months, however, the most prominent changes are to be found mainly in the connective tissue elements. The cervix is composed mostly of fibrous tissue, and the individual cells increase in size and multiply in number. The muscle plays a secondary role, as recently emphasized by Danforth,³ but its cells also hypertrophy and reach their maximum by about the third month. The most striking finding at this early stage is a tremendous increase in the number of blood vessels and lymphatics, and this continues throughout the whole of pregnancy, so that eventually the cervix becomes a soft boggy structure comparable to "erectile tissue." There is a considerable invasion of the mucosa with leucocytes, wandering cells, and plasma cells, but Stieve failed to find any clear evidence of decidua formation. The occurrence of islands of deciduallike cells, however, were described by von Franqué,¹ Ulesco-Stroganoff,⁴ and others.

During early pregnancy there is an increased activity of the cervical glands. The individual cells increase in height, proliferate, and there is a marked production of mucus. This change is progressive throughout pregnancy, but does not become striking until after the twelfth week. From then on the glands increase in number, invade the substance of the cervix, and project into the cervical canal. The average depth of the glands in the nonpregnant cervix is from 1 to 2 mm., but during gestation they measure from 4 to 6 millimeters. The result of this proliferation means a marked increase in the radial measurement of the cervix, half of which is now composed of mucosa. The extension of the glands into the cervical lumen throws the mucosa into manifold folds which form the *arbor vitae*. It has a very distinct honeycomblike appearance, with numerous projections into the cervical canal. These changes, if accepted as the normal picture, are of especial importance in interpreting the significance of the so-called cervical erosion of pregnancy (Figs. 1 and 2).

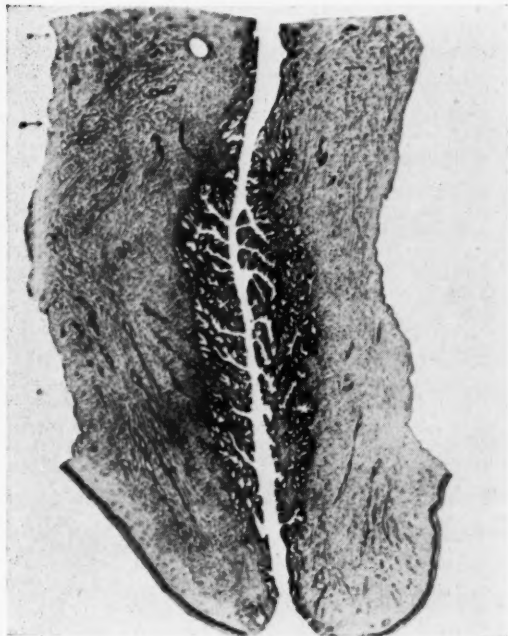


Fig. 1.—Longitudinal cross section of normal nonpregnant cervix uteri. After Stieve.²

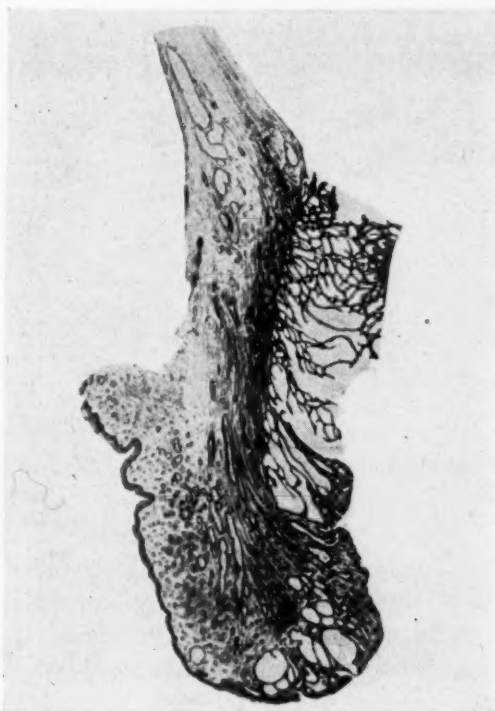


Fig. 2.—Longitudinal cross section of cervix uteri during eighth month of gestation. After Stieve.²

So-Called Cervical Erosion During Pregnancy

Most textbooks of obstetrics make a reference to the frequent occurrence of erosions; especially in multiparas, but fail to offer much more information. In order to obtain some data as to their occurrence, a series of 119 consecutive private patients was analyzed. It is seen from Table I that at the first prenatal visit an erosion was observed in fifty-seven, or 48 per cent, of all groups. There was little difference between primigravidae and multigravidae, since an erosion was found in thirty-seven of seventy-one of the former and in twenty of forty-eight of the latter. If not significant, it is at least of interest that a definite difference was observed between the patients seen early in pregnancy and those who reported for their initial visit in the later months. Of fifty-one first seen during the first twelve weeks seventeen, or 33 per cent, had a cervical erosion while thirty-four, or 66 per cent, did not, while of sixty-eight seen in subsequent months forty, or 59 per cent, had an erosion and in twenty-eight, or 41 per cent, none was demonstrable. Since the effect of labor as a causative factor in the production of erosions is not known, a comparison of findings during the prenatal period and at postpartum examination are not of much value. Nevertheless, of seventy-nine patients seen both before and after delivery forty-four, or 55 per cent, had an erosion during the course of gestation while 65, or 82 per cent, presented this lesion when seen six to eight weeks post partum.

TABLE I. INCIDENCE OF SO-CALLED CERVICAL EROSIONS AT FIRST PRENATAL VISIT IN A SERIES OF 119 PRIVATE PATIENTS

MONTH OF PREGNANCY	GRAVIDA I		GRAVIDA II OR MORE		TOTAL	
	EROSION	NO EROSION	EROSION	NO EROSION	EROSION	NO EROSION
2	11	22	6	12	17	34
3	10	6	5	5	15	11
4	3	0	1	7	4	7
5	6	2	3	0	9	2
6	2	1	1	3	3	4
7	2	0	3	0	5	0
8	3	3	1	0	4	3
9	0	0	0	1	0	1
Total	37	34	20	28	57	62

The gross appearance of a cervical erosion during pregnancy is familiar to all of you. It is essentially a very shallow ulcer with fairly clear-cut edges. Its size varies greatly for it may be a circular lesion one to 2 cm. in depth about the external os or it may occupy only a small segment or again it may extend far up on the portio vaginalis. The base may be smooth or have a granular appearance, and when there is a concomitant infection varying numbers of Nabothian follicles stand out as small yellow points. Its flaming red color is very characteristic, and is especially pronounced when the vaginal mucosa assumes the deep purplish hue so characteristic of pregnancy. It usually bleeds readily on the slightest manipulation.

A diagnosis of erosion of the cervix was made in thirty-two patients of this series, and it was based both on the clinical features of the gross lesion and on

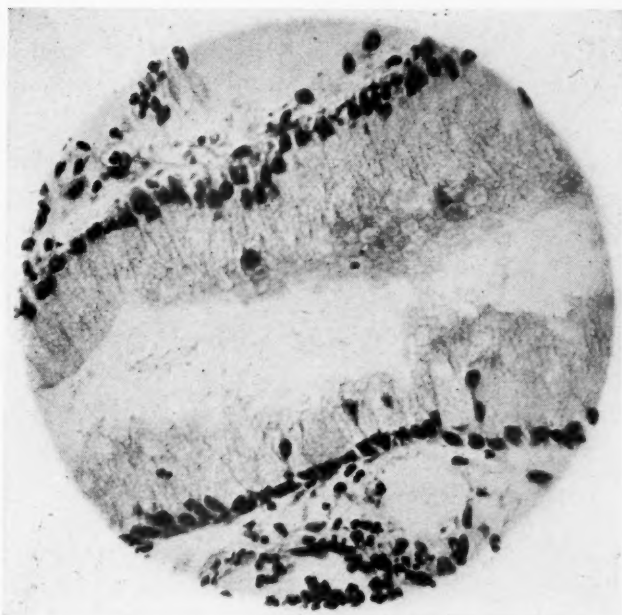


Fig. 3.—Characteristic high cylindrical epithelial cells lining cervical glands during gestation.

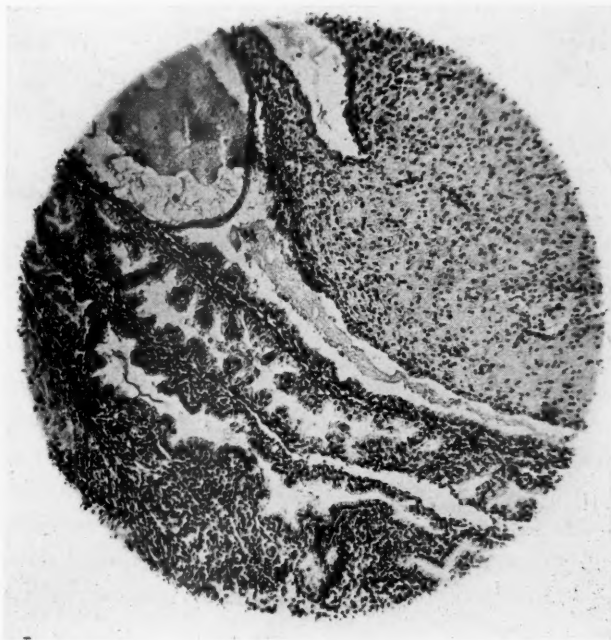


Fig. 4.—Active proliferation of cells lining cervical glands during pregnancy result in stratification, and there are small projections into the lumina. This photomicrograph shows decidual reaction of the stroma on the right.

the histopathologic examination. In 19 cases there were no associated symptoms, and the erosion was discovered on routine examination. Frank bleeding, usually of spontaneous origin, was mentioned in six cases, while "spotting" or a blood-tinged discharge occurred five times, and in two instances the patients complained of an unduly profuse white discharge.

The histologic examination showed a wide variety of changes at the sites of the erosions and they may be considered under separate headings: (a) adenomatous proliferation of the glands, (b) papillary outgrowths, (c) edema and increased vascularity, (d) infiltration with inflammatory cells, (e) epidermidization, hyperactive basal cells and hypertrophy of squamous epithelium, and (f) formation of decidua.

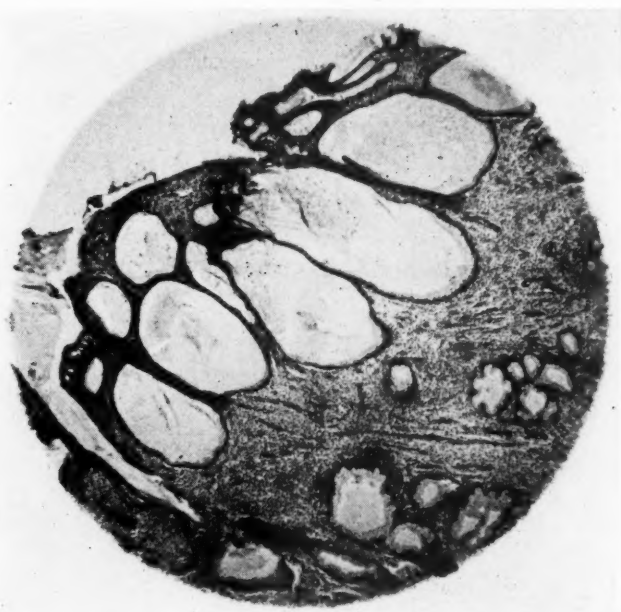


Fig. 5.—Adenomatous proliferation with many cystic glands are a characteristic finding in cervical erosions during gestation.

(a) *Adenomatous proliferation of the glands* is the most striking change observed in cervical erosions during pregnancy and is probably the basic structure of this lesion. The lining cells are of a very high cylindrical type (Fig. 3) and increase to such an extent that often they become stratified and form small projections into the lumina of the glands (Fig. 4). The glands themselves increase greatly in number, and interspersed among those with this type of epithelium may be found many distended cystic structures with the lining cells of the low cuboidal variety. These glandular formations are not only seen at the surface but extend into the substance of the cervix and may reach a depth of as much as 6 to 8 mm. (Figs. 5, 6, 7). The covering epithelium is invariably of the high cylindrical cell type but it may also alternate with patches of squamous epithelium.

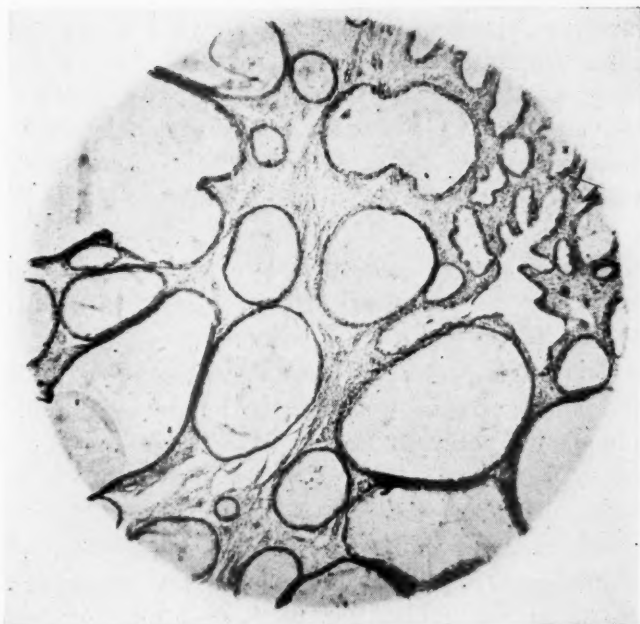


Fig. 6.—Cystic glands in adenomatous proliferation accompanying cervical erosion during pregnancy.

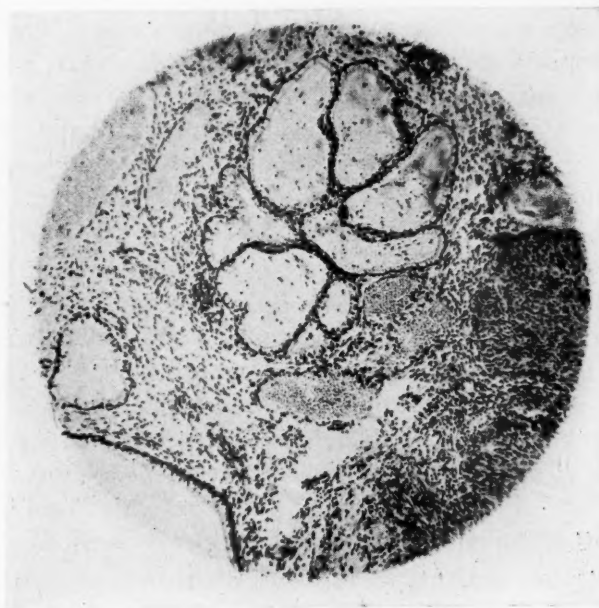


Fig. 7.—Adenomatous change in erosion with basal cell hyperactivity of surface squamous epithelium on the right.

This adenomatous process was demonstrable in twenty-four of the thirty-two specimens. Among these an intense cervicitis only occurred five times and a moderate infiltration with leucocytes, plasma cells and histiocytes occurred in seven. The marked glandular process was accompanied by papillary outgrowths, as described below, in ten instances. There was a hypertrophy of the squamous epithelium twice, and six times there was either a hyperactivity of the basal cells or epidermidization. In six cases islands of decidua-like cells were noted, and in one instance this change was widespread throughout the whole microscopic section.

In two biopsies no glandular elements were seen. Of these, there was an extensive cervicitis in one, moderate round cell infiltration in one, hypertrophied squamous epithelium in one, and islands of decidua in two.

(b) The second characteristic feature involving the cylindrical epithelium was an extensive *papillary outgrowth* such as occurs in "papillary" or "granular" erosions in the nonpregnant (Figs. 8, 9). These formations are generally attributed to a hyperplasia of the connective tissue which lies between the various glands.

There were six instances of the thirty-two where these papillary proliferations were the predominant feature. An extensive cervicitis was present in three, moderate round cell infiltration in four, hypertrophied squamous epithelium once, and in three, islands of decidua were observed.

(c) *Edema and increased vascularity* were particularly in evidence in all instances.

(d) *Infiltration with inflammatory cells* is of especial importance because of the prevalent concept, advanced by Robert Meyer⁵ and others, that all erosions should be considered as the result of an infection. However, a marked cervicitis could be demonstrated in only nine of the thirty-two cases with erosion; in twelve there was a moderate infiltration (usually in limited areas) with leucocytes, plasma cells and histiocytes; while in eleven such wandering cells were only of rare occurrence. This observation is certainly contradictory to Stieve,² who reported this change as a constant finding in the normal cervix during pregnancy.

(e) *The occurrence of a hyperactivity of the basal cell layers of the squamous epithelium and of epidermidization* are of especial importance in view of the search for methods dealing with the recognition of early carcinomatous changes. These abnormal proliferations are especially prone to occur during pregnancy and consequently, there is here a wide field for further investigation and observation. The subject has been discussed many times in the past, for example by Meyer,⁵ Fluhmann,⁶ Novak,⁷ and recently Te Linde and Galvin⁸ again focussed attention on this subject in a paper presented before this Society.

Of the thirty-two patients of this series with erosion of the cervix, an excessive hypertrophy of normal squamous epithelium was seen four times, while epidermidization or hyperactive basal cells appeared in six instances. All of the latter were in the group characterized by an adenomatous proliferation of the glands.

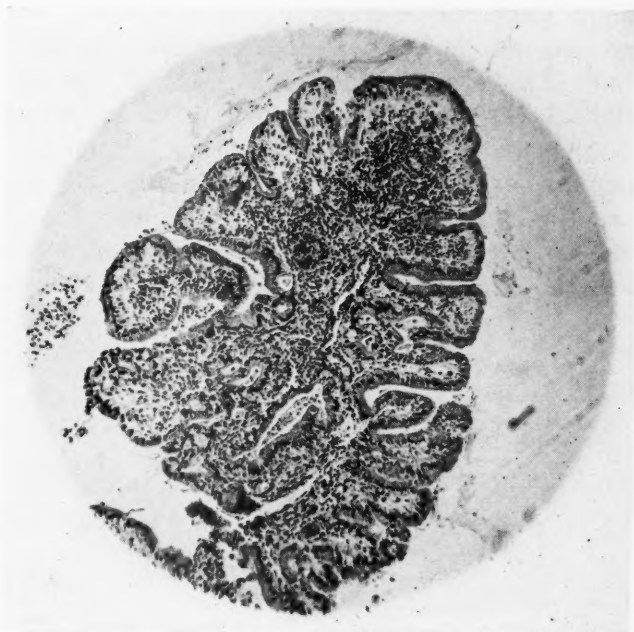


Fig. 8.—Papillary outgrowth in cervical erosion during pregnancy.



Fig. 9.—Papillary proliferation in cervical erosion during pregnancy with marked decidual reaction in one projection at upper center.

When "epidermidization" or "epidermidalization" occurs the cylindrical epithelium is found undermined by developing basal cells. These proliferate, become stratified, undergo vacuolation, and gradually displace the cells at the surface. The individual cells, however, stain evenly, do not show undue variations in size, and mitoses are infrequent (Fig. 10). In the case of basal-cell hyperactivity, an already fully developed squamous epithelium sends out shoots or branches containing immature rapidly proliferating cells which stain irregularly. There may be considerable variation in the size of the individual cells, and many mitotic figures can be found (Figs. 11, 12). It is this picture which presents a difficult problem in differentiation from an early carcinoma. These two processes are thus very distinct entities, but both frequently may be observed in the same specimen.

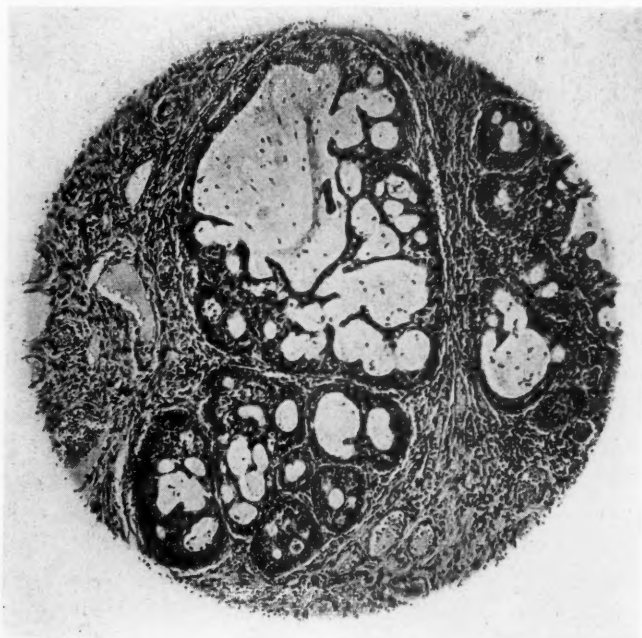


Fig. 10.—Epidermidization of glandular epithelium in cervical erosion during pregnancy.

(f) *Formation of decidua.* Although Stieve² failed to demonstrate the presence of decidua in the pregnant cervix, it has been described by von Franqué,¹ Ulesco-Stroganoff,⁴ and numerous others. In this study an extensive transformation of the stroma into decidua was noted only once, but isolated islands of this tissue occurred in eleven instances. It was generally found near the surface and also in some of the papillary outgrowths (Fig. 9), and, although the cells unmistakably were decidual in nature, they were not as fully developed as those seen in the endometrium.

Etiology of Cervical Erosions During Pregnancy

An analysis of the observations recorded in the preceding section leads to the suggestion that, although some probably result from an inflammatory con-

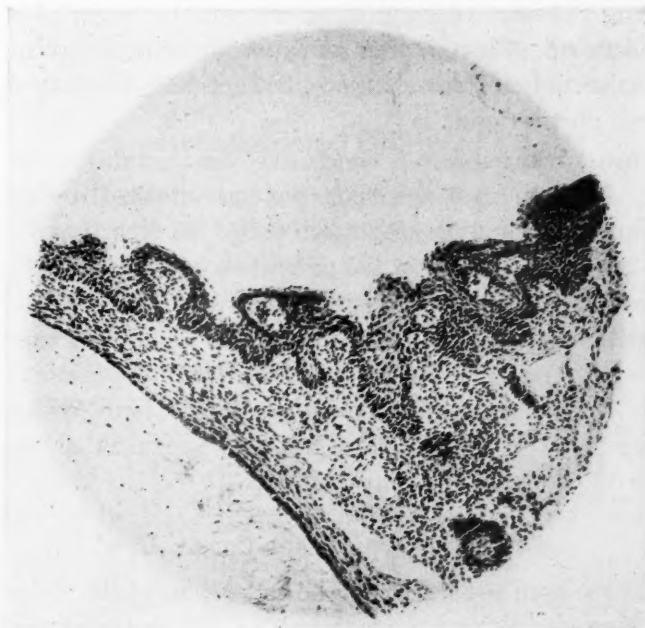


Fig. 11.—Hyperactive basal cell epithelium in erosion during gestation.

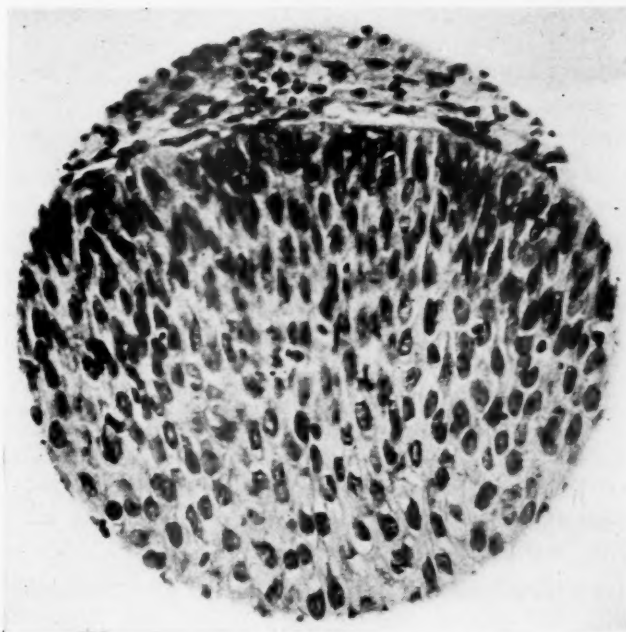


Fig. 12.—High power view of hyperactive basal cells in cervical erosion during pregnancy.

dition which may have existed before the pregnancy, most of the cervical erosions seen during the course of gestation are not the result of a cervicitis, but are a type of adenoma. There is thus an extension of proliferating glands either from the cervical canal or from glands which normally open on to the squamous epithelium of the portio vaginalis.

The evidence advanced is not conclusive, but certain points are worthy of emphasis. (1) In a small series, half the patients had a cervical erosion at some time during pregnancy, a proportion much too great for the normal female population. (2) Only one-third of the patients seen during the first twelve weeks had an erosion, but after this time 59 per cent did have. This observation suggests that erosions appear at about the same time that the maximal normal proliferation of the cervical mucosa occurs. (3) The histologic examination of 32 erosions, all of which (with the exception of the four hysterectomies) were extensive enough to warrant obtaining a biopsy specimen, showed the existence of an extensive cervicitis in only nine instances.

Mucous Polyps of the Cervix Uteri

As might have been predicted, the largest group of the series was of mucous polyps originating either from the external os or from the cervical canal. There were specimens from thirty-seven patients, and their gross appearance and characteristics are so well-known that it is superfluous to enter into any details at this point. It might be mentioned, however, that bleeding occurred only in six instances.

The histologic examination presented a series of pictures which closely resembled those described under "erosions of the cervix," but there were a few notable exceptions. Extensive inflammatory processes were more frequent, and occurred in seventeen of the thirty-seven cases, while a moderate infiltration with round cells was observed six times. The formation of decidua was much more marked and even involved the whole polyp in twelve, while isolated islands of decidualike tissue were seen three times. Epidermidization and hyperactivity of basal squamous epithelial cells were noted in six cases. Fig. 13 illustrates one of the serious problems resulting from this finding. The surface epithelium was either of the cylindrical or squamous type, or both were present at various levels. It is possible that some of these polyps may have been of endometrial origin.

The basic structure of the polyps on histologic examination showed that they could be grouped into four categories according to the behavior of the cylindrical cell epithelium.

1. In thirteen instances the polyp was essentially an adenoma with marked proliferation of glands, many of which were dilated and cystic.

2. Ten were mostly papillary offshoots such as described in the section on cervical erosions.

3. A moderate proliferation of the glandular elements, in fact, scarcely more than one would expect in a normal cervix, was noted seven times.

4. In seven cases no glands were seen in the sections studied. These polyps were composed mostly of a core of connective tissue and some muscle cells, with a surface epithelium. Extensive decidua formation was demonstrable in six, a marked inflammatory reaction in five, and several showed areas of necrosis.

Endometrial Polyps

Three polyps with their base high in the cervical canal have been classified as endometrial in character and doubtless arose from the isthmus of the uterus. The two criteria on which this diagnosis was based were (a) the fact that they were composed almost entirely of decidua and the individual cells, as compared to the usual cervical polyps, were larger and stained more regularly and deeply, and (b) the few glands present were not of the cervical type but resembled glands from the isthmus in their usual incomplete stage of secretion.



Fig. 13.—Hyperactive basal cells from a cervical polyp removed during early pregnancy. Three observers considered this lesion as of a carcinomatous nature, but some doubt was entertained and a subsequent biopsy of the cervix from the region of the base of the polyp did not show any malignant change. The patient was allowed to continue to term and had a normal delivery and postpartum course. Four years later there is no demonstrable lesion of the cervix. (Private patient of Dr. Frank Norris.)

Carcinoma Cervicis Uteri

The subject of cancer of the cervix uteri during pregnancy is far beyond the limits of this paper, but because of its very nature some mention must be included. In 1934, Emge⁹ presented before this Society a report on six cases of cervical cancer in pregnancy which had been observed at Stanford. Some details are given in Table II and, of the six, one had died after four years and two were known to be alive five and six years later. No further information

TABLE II. STANFORD SERIES OF CERVICAL CARCINOMAS ASSOCIATED WITH PREGNANCY

NO.	LAB. NO.	AGE	GRAVIDA	PARA	MONTHS PREGNANT	TYPE CARCINOMA	DEGREE MALIGNANCY	CLINICAL CLASSIFICATION	TREATMENT	RESULT
1	5177	25	iii	ii	2	Squamous	Immature	Inoperable	Radium	Died end of fourth year
2	A3918	32	vi	v	7	Squamous	Immature	Border	Radium x-ray	Alive 5 years later
3	3292	38	v	iv	4	Adenocarcinoma	Mature	Operable	Hysterectomy	Alive 6 years later
4	A3496	36	iii	ii	4	Adenocarcinoma	Mature	Border	Hysterectomy	Died 7 years later
5	A3565	37	i	i	Term	Squamous	Midmature	Operable	Radium	Alive nineteen years later
6	A4962	38	i	0	3	Squamous	Immature	Operable	Radium	Died 9 years later
7	B8431	26	iv	ii	6½	Squamous	Immature	Operable	Radium hysterectomy	Alive 6 years later
8	C6118	36	ii	ii	3	Squamous	Mature	Operable	Radium	Died gas bacillus infection during treatment
9	C6593	27	i	0	2	Squamous	Mature	Operable	X-ray radium laparotomy for ectopic	Alive 6 months later
10	C6825	36	v	iv	6	Squamous	Midmature	Operable	Hysterotomy radium	Under treatment May, 1947

could be obtained on these, but of the other three, one died after seven years, one after nine years, and one has survived and is in good health after nineteen years.

There are four cases to add to the series, three of which are so recent as to offer little practical information. However, all four were seen early in the course of the disease and were diagnosed as in stage I or "operable." The first (No. 7 in table) had an immature squamous cell carcinoma, was seen at six and one-half months, and has survived six years after treatment with both radium and hysterectomy. The second (No. 8), first seen at six months, was transferred to the County Hospital and tragically died of a gas bacillus infection following the first radium application. The third (No. 9) was recognized six months ago as having an early cancer of the cervix, but shortly after radium therapy had been initiated her complaint of a two months' period of amenorrhea was found to be attributable to an ectopic gestation and a laparotomy for this condition was performed. The fourth (No. 10) is a very recent patient who reported with an early cancer of the cervix and pregnancy at six months. A hysterotomy has been performed and she is now under radium therapy.

Summary

This report is an analysis of eighty-nine specimens obtained from the cervix uteri in a group of women at all stages of gestation. Four were obtained by hysterectomy and the others by removal of a lesion recognized grossly or by a biopsy of the cervix.

Gross and histopathologic examination revealed that mucous polyps of the cervix were found in thirty-seven, erosion of the cervix in thirty-two, carcinoma of the cervix in ten, condyloma acuminata in five, endometrial polyps in three, and leucoplakia in two.

A histopathologic analysis of thirty-two so-called "erosions of the cervix" extensive enough to warrant obtaining a biopsy specimen, suggests that this lesion should be considered as an adenoma of the cervix rather than an inflammatory condition.

As a matter of record, some details are given of the ten cases of carcinoma of the cervix uteri seen during pregnancy in the Department of Obstetrics and Gynecology of the Stanford Medical School.

My thanks are due to Mr. Pierre Lassègues for the photomicrographs, and to Mrs. Joseph S. Rogers for her assistance in the preparation of the manuscript and the clinical follow-up studies.

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Discussion

DR. WALTER T. DANNREUTHER, New York City.—We have all seen pathologic lesions of the cervix from time to time in pregnant women, but perhaps have failed to realize that there was much difference in their character from similar lesions encountered in the non-pregnant. It would be interesting to know how high an incidence the 89 cases reported by Dr. Fluhmann represents. Since 40 were private patients, the percentage obviously cannot be calculated, but perhaps Dr. Fluhmann can tell us the total number of obstetrical patients in the clinic among whom the remaining 49 cases were found.

It is not surprising that cervical polypi and erosions constitute a little more than 75 per cent of all the pathologic conditions discovered, because these occur so frequently in young women. And since there is increased physiological activity, hyperemia, hypertrophy and endocervical glandular stimulation during pregnancy, it is natural that pre-existing lesions should be involved in these alterations.

Dr. Fluhmann found 57 erosions in 199, or about 50 per cent, of his own private patients. Sometimes these erosions are so massive that the gross appearance closely resembles carcinoma. I have seen two such cases with a shaggy, extensively papillomatous surface which bled easily, and both showed the same adenomatous changes mentioned by Dr. Fluhmann. Incidentally, both patients miscarried in the sixth month. I agree with the essayist that all cervical erosions do not show evidence of infection and endocervicitis, and that decidual reaction of the stroma cells is not a constant finding.

Cervical carcinoma occurring in the pregnant uterus presents a serious clinical problem, and each case confronts us with an individual therapeutic question. However, it seems logical always to regard the carcinoma as of major importance.

DR. T. K. BROWN, St. Louis, Mo.—Dr. Fluhmann has emphasized the importance of careful inspection of the cervix in prenatal care. He has gone further than this and obtained the histopathologic findings in a series of 89 such cases. Most of us would probably have made similar observations and have treated the abnormality by some simple procedure such as cauterization, coagulation, or evulsion. The author went further than this and obtained biopsy specimens when indicated by suspicious areas.

Analysis of the diagnoses in this series revealed ten cases of carcinoma of the cervix. Four cases have been diagnosed since 1934. On the service at Washington University, Hobbs has reported four cases of carcinoma during pregnancy in a similar period of time.

The changes in the cervix during pregnancy described by Stieve, Danforth, and Schwarz indicate that there is hypertrophy of the cells and increase in the number of blood vessels and lymphatics. The proliferation of the glandular structures of the cervix during pregnancy is also marked. It seems that this increase in bulk of the tissues in this area can account for the development of cervical erosion during pregnancy by simple eversion of this excess tissue through the external os. These changes persist in varying degrees into the puerperium.

Another pathologic condition which may be encountered during pregnancy is endometrial implants on the cervix and vaginal mucous membranes. These areas may bleed and present an appearance very similar to carcinoma of the cervix.

I should like to ask the essayist how his plan of treatment of cases with carcinoma of the cervix associated with pregnancy varies according to the stage of pregnancy at which the patient is first observed.

DR. EMIL NOVAK, Baltimore, Md.—Dr. Fluhmann has presented us with an interesting study on a subject concerning which our knowledge has been very incomplete. While it might be expected that the cervical mucosa, being a Müllerian derivative, is under the hormonal control of the ovarian hormones, I know of only one really worth-while study of its cyclical histology, that of Sjövall of Stockholm.

Again, since the vaginal mucosa is so responsive to hormonal, more particularly estrogenic, influence, why should this not apply also to the squamous epithelium of the pars vaginalis, which is its direct continuation? And why may not such an estrogenic stimulus explain some of the milder instances of "basal cell hyperactivity," which I personally feel

have been overaccented in the feverish search for the earliest phases of cervical carcinoma? It would seem that this point could be clarified by sufficiently extensive studies of biopsies or surface scrapings of cervixes at various phases of the cycle.

Decidual reaction in the cervix is not a very common finding, but over the years we have seen a considerable group of such cases in our laboratory. As to erosions and polyps, it is of practical clinical importance to remember that vascular lesions of this sort are a not uncommon cause of bleeding during pregnancy. Since many patients interpret almost any vaginal bleeding as menstruation, such lesions are always to be thought of when women report that they "menstruate" even though pregnant.

DR. WILLARD ALLEN, St. Louis, Mo.—I have recently had the privilege of seeing a patient with profound, extreme erosion of the cervix occurring during pregnancy. Two competent gynecologists had already made a provisional diagnosis of carcinoma of the cervix without being aware of the pregnancy. We had to avail ourselves of the rabbit test to be certain of the diagnosis of pregnancy. The lesion was of the cauliflower type of carcinoma of the cervix and measured about 6 cm. in diameter. The only thing that made me suspect that the lesion was probably not malignant was the difficulty encountered in making a satisfactory biopsy.

I want to emphasize the rapidity of the changes in the cervix. This patient was less than two months pregnant when first seen. She aborted spontaneously at about three and one-half months of pregnancy. I saw her three weeks following the abortion. At that time there was no erosion, nothing but a deep laceration extending up to the internal os and thereby exposing the cervical canal so that what we had seen and thought was carcinoma was nothing but the changes of normal pregnancy made visible by the old laceration.

I would like to ask how many of Dr. Fluhmann's patients had deep cervical tears so that he could see far into the cervical canal and not merely into the os?

DR. GEORGE W. KOSMAK, New York City.—I would like to ask if Dr. Fluhmann could find a more suitable and descriptive term for what he calls "erosions." It always offends my editorial sense to see that word used.

DR. KARL MARTZLOFF, Portland, Oregon.—It is embarrassing to be the only one to voice a dissenting note in this otherwise serene discussion, but I could see no anatomic evidence of bona fide cervical erosion in Dr. Fluhmann's sections. The histologic appearance of his material is characteristic of the commonly observed circumostial vermilion zone. I would therefore like to ask Dr. Fluhmann how he uses the term "erosion." It is rather tragic to see patients possessing a vermilion area about the external os of the cervix, who have been informed that they have an ulcer which needs cauterization or some other form of therapy. This often is the beginning of a course of questionable cervical tinkering to an area which is certainly not an erosion and possessed of no serious pathologic significance. Occasionally, these areas can have their superficial epithelium knocked off by light trauma, and they may then bleed readily.

Did any of Dr. Fluhmann's erosions show actual loss of substance with a fibrinocellular membrane covering the site of the epithelial loss? This, it seems to me, is the minimal requirement for diagnosis of a bona fide benign erosion.

I would also like to ask whether the carcinomas that Dr. Fluhmann observed were well developed so that one might detect them readily by inspection, or did they belong to the so-called noninvasive types of cancer?

It should also be mentioned that polypoid hyperplasia of the mucosa of the cervical canal may occur in the absence of pregnancy. I know of nothing that is more confusing to the naked eye observation of the cervix than this alteration which may grossly resemble cancer but which on histologic examination shows a benign polypoid change.

DR. FLUHMAN (Closing).—I am very sorry that I cannot use these cases from a statistical standpoint as they are merely 89 specimens found at random in the laboratory. Many of them were from private practice, and since many of our men deliver their pa-

tients in other hospitals, it would have been impossible to calculate the total number of obstetric cases from which the specimens were obtained.

I was interested in hearing Dr. Brown speak of endometriosis. We have seen it in the cervix and vaginal wall, but not during pregnancy.

The treatment of cancer during pregnancy is far beyond the limits of this paper. We would certainly treat a cancer early in pregnancy very differently from one near term. The last patient noted in Table II was treated with hysterotomy, followed by irradiation. All the cancer patients listed in Table II were proved cases both clinically and histologically. None could possibly be considered as representing the so-called preinvasive type of lesion.

In no instance did an abortion result from the manipulation incident to obtaining a biopsy of the cervix. However, since it is necessary to cauterize the area from which the specimen is taken and a dirty slough results, the possibility of infection is present especially if an abortion should result. For this reason, no biopsies were performed purely to gratify scientific curiosity, and in all cases the visible lesion was regarded as suspicious.

I cannot tell for certain if any of the biopsies were obtained from the cervical canal in the presence of extensive lacerations, but if so they must have been too few in number to change the general picture described in my paper.

I am in full agreement with Dr. Kosmak and Dr. Martzloff that the term "erosion" is a bad one, but it is in such general usage that any attempt to introduce a new one would probably not be successful. It, of course, refers to the gross appearance of the lesion and, as I have indicated, there are wide variations in the histologic picture.

CERVICAL DYSTOCIA, WITH SPECIAL REFERENCE TO THE FIBROUS NATURE OF THE CERVIX*

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(From the St. Louis Maternity Hospital)

NOTABLE by its absence is the well-recorded information concerning cervical dystocia in the English and American literature. The standard textbooks of obstetrics give little more than a passing mention to the condition and in the minds of many authorities little credence is given to its actual occurrence in the course of labor. When one has been confronted by the dramatic course of events such as presented in Case 1, then it is most difficult to concur with the latter group in the opinion that denies the existence of the cervical dystocia entity.

Diligent searching of the literature reveals only two outstanding reports in English on the subject during the past twenty years. Of particular significance is the fact that in considering the subject, the authors stress the importance of fibrosis of the cervix as a cause of cervical dystocia. In explaining the etiology and pathology of the condition Mathieu and Schauffler imply that the rigid and stenosed cervix is the end result of chronic irritation that causes destruction of the cervical "specialized muscle and elastic fibers" and replacement of these tissues by nonexpansile scar tissue cells. All other things being equal, the ability of the cervix to dilate is directly proportionate to the amount of muscle and elastic tissue elements as compared to the fibrous tissue content. Sackett in his report also emphasizes the rigid stenotic cervix that follows various traumas, irritations, and infections, in addition to stressing a constitutional deficiency as another general cause for cervical dystocia. He states, "Since active dilatation, retraction, and effacement of the cervix depend upon its intrinsic smooth muscle and autonomic nerves, this function may be weakened by underdevelopment, and constitutional and endocrine deficiency. It is further compromised and resisted by scar tissue replacement of the parenchyma following trauma or disease. This fibrosis also obviously hinders passive dilatation by the bag of waters and presenting part."

Such is the sentiment in the two most complete reports of the last twenty years concerning cervical dystocia. In both there is a definite implication that the origin of the condition resides in the replacement of elastic fibers and/or muscle fibers by fibrous tissue. In the recent report by Danforth, and the material to be presented below, it becomes quite obvious that the entire subject of cervical rigidity during labor must be reappraised to conform with the anatomic and histologic facts. The cervix is a priori predominantly of a fibrous nature and, therefore, it is difficult to visualize that in cervical stroma the addition of more akin fibrous tissue, from whatever cause, would lead to the occurrence of the impressive train of events recognized in some quarters as cervical dystocia.

*Presented at the Seventieth Annual Meeting of the American Gynecological Society, the Seigniory Club, Montebello, Quebec, June 17 to 19, 1947.

CASE 1.—H. D., Hospital No. 52733, was a 33-year-old Negro primigravida admitted to the St. Louis Maternity Hospital on March 1, 1947. Her expected confinement date from the menstrual history was January 14, 1947, but the fetal heart was first definitely heard in November, 1946. Fetal movements were felt by the patient in October, 1946. Beginning two weeks prior to admission, painless uterine contractions were noted and the membranes had ruptured spontaneously on the day of admission. The antepartum course was entirely uneventful, with an adequate pelvis as determined by pelvimetry. Past history, family history, and laboratory findings were noncontributory. Physical examination at time of admission was essentially normal, with a McDonald of 39 cm. and a vertex presentation, left occipitoposterior, floating.

During the first thirty-six hours after admission uterine contractions were irregular in occurrence and of poor quality. Following this the contractions occurred every five minutes, but were of twenty second duration. Examination revealed head dipping, and the cervix effaced was dilated 1.5 cm. Several hours later the contractions were of excellent quality every two to three minutes, lasting thirty to forty seconds, and this lasted over a period of six hours during which time she received 150 mg. of demerol, and the presenting part descended to the level of the ischial spines. It was noted, however, that no additional cervical dilatation had occurred during the latter period of active labor. Active labor continued for nine hours more without any progress of cervical dilatation or descent of the presenting part.

Because of the poor quality of contractions that ensued, and maternal fatigue, the patient was given morphia, parenteral fluids, and a rest of six hours was afforded. Active labor followed the rest interval, and examination revealed that the cervix was becoming more firm and thick. Irregularity of the fetal heartbeat prompted a vaginal examination, at which time it was noted that the cervix was about 4 cm. dilated and of the consistency mentioned previously. Upon pushing the head up a bit from its S + 1 station, the fetal heart again became regular and no further procedure was attempted. Four hours of fair labor followed, during which time the head descended below the spines, but the cervix did not dilate, and further supportive fluids were administered to the patient. The superior sagittal suture remained in the right oblique, and the position was thought to be right occipitoanterior.

Approximately forty hours after the onset of good labor the patient was delivered spontaneously of a normal living female infant weighing 3,450 Gm., who expired sixteen hours after birth. Autopsy of the infant revealed no gross cause of death. Examination of the cervix after delivery revealed that the infant had been delivered through an 8 cm. hemisecting tear of the anterior face of the cervix that ran from a superior left aspect to an inferior right lateral aspect. The os was intact and 4 cm. dilated; and the consistency was described as being "tough and undilatable." The laceration was repaired with interrupted chromic catgut sutures. The patient's postpartum course was uneventful, and the patient was discharged from the hospital on her eighth postpartum day, at which time the cervix was found to be firm, fibrous, and the laceration was healing well.

CASE 2.—M. C., Hospital No. 39233 (private patient of Dr. F. P. McNalley), was a 36-year-old white gravida ii, para 0, who was admitted to the St. Louis Maternity Hospital on April 4, 1947. From the patient's menstrual history, the estimated date of confinement was March 31, 1947. Her first pregnancy had terminated at three and one-half months by a spontaneous abortion. The patient had weighed 211½ pounds when seen during the first trimester, and at term weighed 213½ pounds. By pelvimetry the patient possessed a normal pelvis, and the routine laboratory studies were not remarkable. During the

antepartum period she had been given 0.060 Gm. of thyroid extract daily, and during the second and third months of the pregnancy she was given 10 mg. of pregnenolone twice a day orally because of history of previous abortion. Remainder of past history and family history were noncontributory. Physical examination upon admission was essentially normal, with membranes intact, McDonald of 35 cm., and presenting part vertex, left occipitotransverse, floating. The patient had been having irregular uterine contractions prior to admission that continued irregular in interval and intensity for almost twenty-four hours, and she was thought to be in early labor.

During the next four days the patient had an occasional mild contraction, and the membranes ruptured spontaneously on the fifth day following admission. Three days after the membranes had ruptured vigorous labor began. Vaginal examination at this time revealed that the presenting part was floating and the cervix was 2 cm. long and admitted a fingertip. The labor continued unabated for seventeen hours, and a vaginal examination was done. The head was engaged to 1 cm. above the ischial spines, left occipitoposterior, and the cervix was effaced except for a thick margin, and there was 4 to 5 cm. dilatation present. Analgesia and amnesia was commenced at this time and maintained for the duration of labor using demerol and hyoscine. Labor continued vigorously with excellent regular contractions every three minutes lasting fifty to sixty seconds for three and one-half hours longer, at which time findings by vaginal examination were as before. Kielland forceps were applied through the partially dilated cervix, and the head was rotated to a left occipitoanterior position and held in that position without traction for the next one and one-half hours while labor progressed. The forceps were removed, and excellent contractions continued for another one and one-half hours, when vaginal examination showed the head to have reverted to the left occipitoposterior position with the most dependent portion just below the level of the ischial spines. The cervix was approximately 6 cm. dilated, and a gentle attempt was made to increase the dilatation normally. Two hours later vaginal examination was again done. The cervix possessed a "good" rim, and the left occipitoposterior head had made no further descent. Kielland forceps were again applied through the incompletely dilated cervix, and the head was rotated to an anterior position and held while the anterior lip of the cervix was gradually pushed over the occiput manually. The Kielland forceps were removed and Schwarz forceps were applied. Delivery was effected by low forceps from left occipitoanterior position over a right mediolateral episiotomy twenty-eight hours after the onset of active labor. The infant was a normal male weighing 3,740 Gm. who required no resuscitation. Examination of the lower genital tract after delivery revealed no evidence of injury. The postpartum course was uneventful, and the patient and infant were discharged from the hospital on the tenth postpartum day.

CASE 3.—G. H., Hospital No. 50583 (private patient of Dr. W. D. Hawker), was a 33-year-old primigravida who was admitted to the St. Louis Maternity Hospital on April 20, 1946. From the patient's menstrual history the estimated confinement date was April 23, 1946. When first seen by her obstetrician in February, 1946, physical examination revealed a tender 3 inch myoma in the region of the right cornua of the uterus. Also, the patient had a 2 inch shortening of the right leg as a sequela to anterior poliomyelitis. In November, 1945, a myomectomy had been performed at a Naval Hospital in California. Pelvic measurements were essentially normal. The remainder of the antepartum course, past history, and family history were noncontributory. Routine laboratory procedures were not remarkable.

Upon admission to the hospital, the patient had had uterine contractions for two hours. Physical examination was normal except for the presence of

shortening of the right leg and a recently healed lower right rectus abdominal scar. The presenting part was vertex, engaged, and left occipitotransverse. Contractions were regular every eight minutes, lasting thirty seconds. Within two hours the contractions were regular and of good quality, occurring every four to five minutes, and of forty-five second duration. Vaginal examination found the membranes intact, the cervix approximately 50 per cent effaced, and 2 cm. dilated, and the head at the level of the ischial spines in a left occipitotransverse position. Amnesia and analgesia were instituted with barbiturates and hyoscine. Labor continued with contractions as previously noted, and rectal examination revealed the cervix only 1 cm. thick two hours later, while other findings were essentially as before. Because the contractions became somewhat less frequent during the sixth hour, two minims of infundin in divided doses were given, causing the resumption of vigorous labor. Vaginal examination during the seventh hour revealed the cervix completely effaced, but the other findings were as previously noted.

During the next five hours contractions were vigorous, but vaginal examination found cervical dilatation as before of approximately 2 cm., and the cervix was described as "thin and moderately soft." At this time the membranes were ruptured surgically. There followed a period of twelve hours of active labor with excellent regular contractions, during which time the cervix dilated to approximately 6 cm. and the head in left occipitotransverse position descended to a station 1 cm. below the level of the ischial spines. A note was made that the anterior lip of the cervix was becoming edematous. No progress was noted during the next two hours, and, because of signs of maternal fatigue, morphia and parenteral fluids were administered.

Irregular, infrequent, mild contractions occurred during the next eighteen hours, after which time examination revealed no change in the cervical dilatation or consistency. However, the head had rotated to a left occipitoanterior position. Fair to good frequent contractions ensued, after four hours of which the head descended to an S + 2 station with contractions and 8 cm. of cervical dilatation was present. A midforceps application was made through the incompletely dilated cervix followed by traction and Dürrssen's incisions of the tough remaining rim of the cervix. A living normal female infant weighing 3,840 Gm. was then delivered by midforceps from left occipitoanterior position over a right mediolateral episiotomy that extended during the delivery through the rectal sphincter. The cervical incisions were repaired with interrupted No. 1 chromic catgut sutures. The total time elapsed since the onset of labor was approximately forty-eight hours. After an uneventful postpartum course, the patient and infant were discharged on the fourteenth postpartum day.

CASE 4.—Patient of O. S., entered St. Louis Maternity Hospital on Nov. 24, 1942. The membranes ruptured spontaneously before admission. Patient began to have contractions at 3:00 A.M. on November 24, the pains coming every three minutes, lasting sixty seconds or longer, and of strong duration. At 12:20 P.M. hyoscine was started, 2 c.c. being given over a period of three hours. In spite of thick, intense contractions, no dilatation was obtained. The cervix was effaced and there was one finger dilatation at 6:30 P.M. The lower uterine segment had apparently thinned considerably and with a rigid os present it was thought advisable to do a cesarean section. This was performed at 7:30 P.M. on Nov. 24, 1942, doing the low cervical transverse type. Results were good for both mother and infant.

Patient was readmitted on Dec. 27, 1944, in beginning labor. Examination showed the cervix long, and, in view of the fact that the cervix presented a condition similar to that presented before, an elective section was decided upon which was performed on Jan. 2, 1945, with similar good results.

CASE 5.—Patient of O. S., entered St. Louis Maternity Hospital on March 24, 1947, with a breech presentation confirmed by x-ray. Her estimated date of confinement was March 17, 1947. Patient had constant Braxton Hicks contractions for two weeks prior to operation. The cervix was long, pelvic floor very resistant. Both the puborectal portion and the iliac portion of the levator ani muscles were very prominent. The patient was seen on July 27, 1946, for

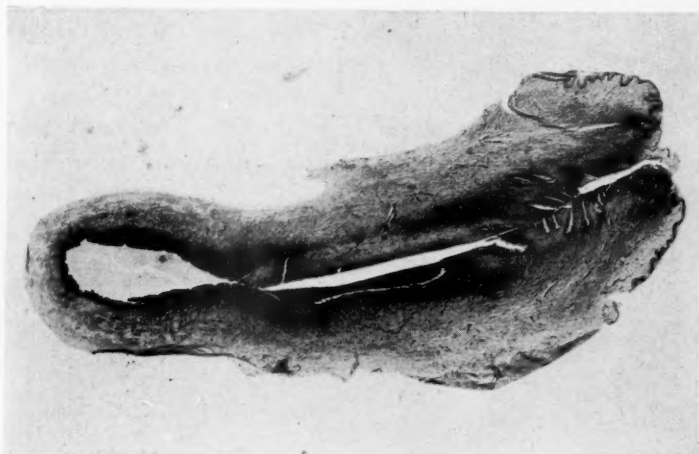


Fig. 1.—The entire section of uterus of a 2-year-old child. Fig. 2 shows the contents of the cervical structure.

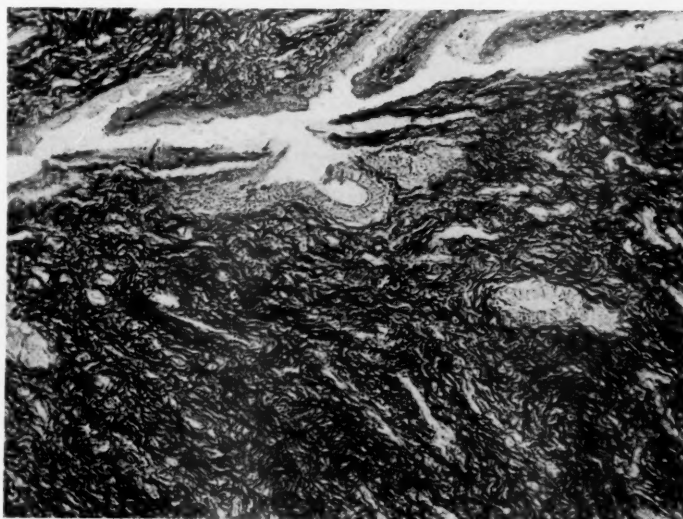


Fig. 2.—Van Gieson stain showing cervical canal, fine black fibular structure, entirely connective tissue.

the first time, having missed her period just two weeks previously. The uterus was soft, but not appreciably enlarged. Pregnancy was suspected which proved correct, so that the onset of the pregnancy was assured.

On March 30, 1947, a low transverse incision was made for section. During the operation it was noted that exposure of the lower transverse incision was not as good as under ordinary circumstances, and after the delivery of the infant the uterus was brought through the abdominal incision to render suturing

more satisfactorily. A very small incision was made (not more than 12 to 13 cm.), and on closing, the uterus fell easily into the abdominal cavity, indicating that it was not a normal-sized uterus. It was suspected at that time that the patient had an infantile uterus and, hence, a primary inertia. This contention was proved without a doubt eight weeks post partum, when examination of the uterus showed it to be definitely smaller in size than a normal nulliparous uterus.

Comment

From the above-mentioned statements it is obvious that in the discussions of the subject it revolves itself entirely on the fibrous nature of the cervix, as put so well by Danforth. Irrespective of what clinical ideas we wish to present on the functional rigidity of the cervix, it would have no place or weight unless Danforth's recent findings were thoroughly discussed. So, therefore, this presentation in short is concerned chiefly with the confirmation of Danforth's findings, to which we can say we perfectly agree.

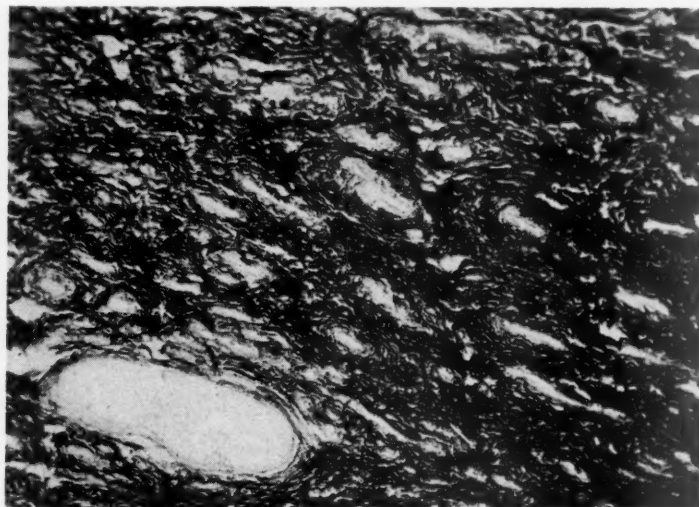


Fig. 3.—Multiparous uterus, aged 50 years. Section near external os. Cervical glands showing black fibular structure entirely connective tissue.

We were a little doubtful of whether the use of old material would suffice for an exact study, but with previous experiences with old fixed material for the body of the uterus, we thought we might try. Amazingly, the material stained perfectly, and as a result we were able to confirm Danforth's work entirely. Of course, our work, as a result of time, was limited to a study of 19 cases. However, we were able to perfectly reproduce our findings with colored photomicrographs. To make a confirmation of Danforth's findings we can do no better than to quote him verbatim.

"The Nonpregnant Uterus.—

"A. Intrinsic structure of cervix and isthmic segment: The appearance of the cervical wall in routine hematoxylin and eosin stains is familiar. It is composed of interlacing strands of fibrillar tissue which take a light pink stain, show

no tendency to strata formation, and, except for the edema which accompanies many cervical lesions, show no significant differences from the uterine wall above the cervix. In some areas the tissue resembles fibrous tissue, in others, smooth muscle. When employing this stain alone, absolute differentiation throughout the entire cervix is considered as impossible.

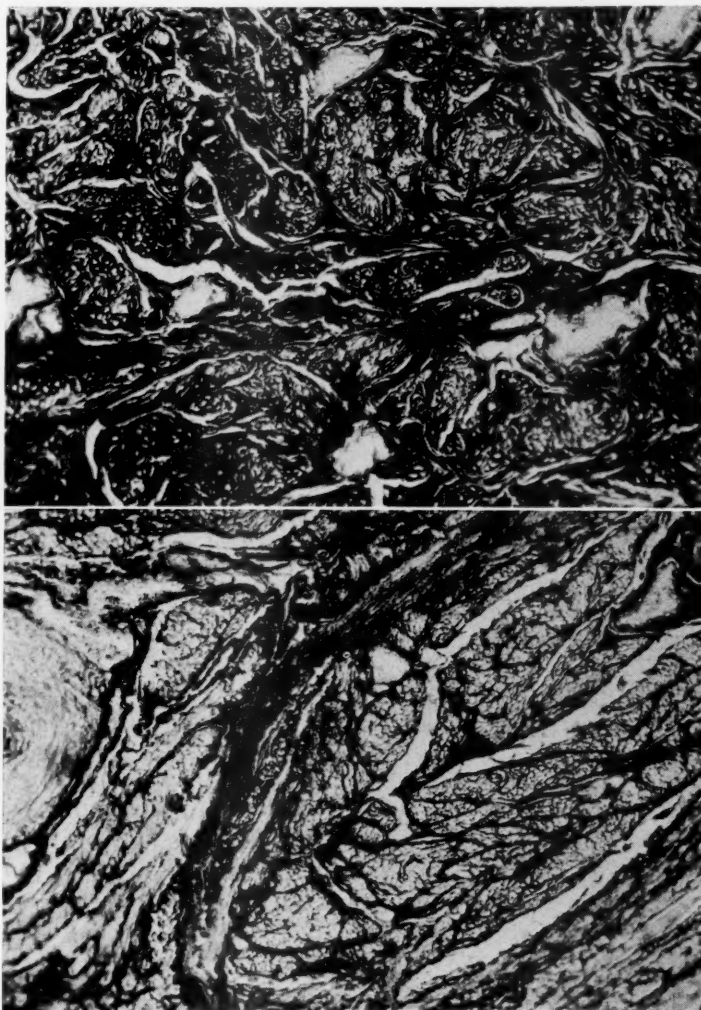


Fig. 4.—Same section taken well up in the cervix showing muscular structure beginning to appear, perhaps 30 per cent.

Fig. 5.—Same cervix outer third higher up, showing beginning predominance of muscular structure.

“A very striking picture is obtained by use of differential stains for fibrous tissue and smooth muscle. The basic structure of the cervix is found to be fibrous connective tissue. In many specimens virtually no smooth muscle can be found. From this extreme, one passes to other specimens in which moderate amounts of muscle are present; occasionally this may reach as much as 40 or 45 per cent though ordinarily it does not exceed 10 or 15 per cent. When muscle does appear in cervical sections, its distribution shows great variability. Ordinarily the muscle fibers are scattered at random throughout the substance of the

cervix. Rarely, they appear in small bundles near the central portion of the tissue, being either isolated or continuous with the muscular tissue superior to the cervix. The inconstancy of such central bundles and their attenuate appearance when they are present make it unlikely that sphincteric possibilities could be attributed to them.

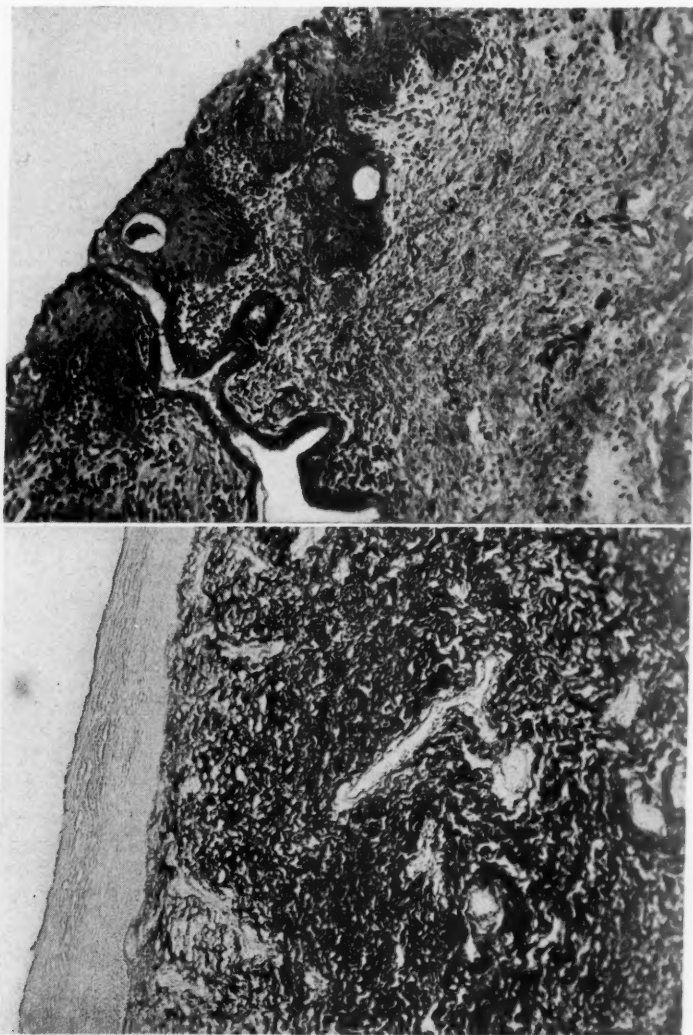


Fig. 6.—Hematoxylin-eosin stain near external os.

Fig. 7.—Practically same field showing practically entire connective tissue with light squamous epithelium to the left.

“Stains for elastic tissue showed the presence of minute and, to the author’s opinion, insignificant amounts of these fibers. The fibers were found to be very sparsely scattered in a haphazard manner throughout the substance of the cervix. As one might expect, they were most abundant in and around the walls of the larger blood vessels. Elsewhere they constitute but a fraction of 1 per cent of the total fibrous tissue of the cervix. Superior to the cervix they were also sparse, being for the most part limited to the outer third of the uterine wall and located in the fibrous tissue separating the muscle bundles.

"The fibromuscular junction: As one ascends the cervix to the region of the histologic internal os, a level is reached where the predominance of fibrous tissue ceases, giving way to smooth muscle. The nature of the transition zone is variable. Sometimes it is abrupt and immediately complete, while in others it may be extremely gradual, occurring almost imperceptibly over the course of 5 or (at most) 10 mm. In some instances the plane of the transition is straight across the uterine wall; but more often the line is a wavy one. It is of interest that not only may the nature of the transition line vary in different portions of



Fig. 8.—Gross specimen cervix of about twenty weeks pregnancy.

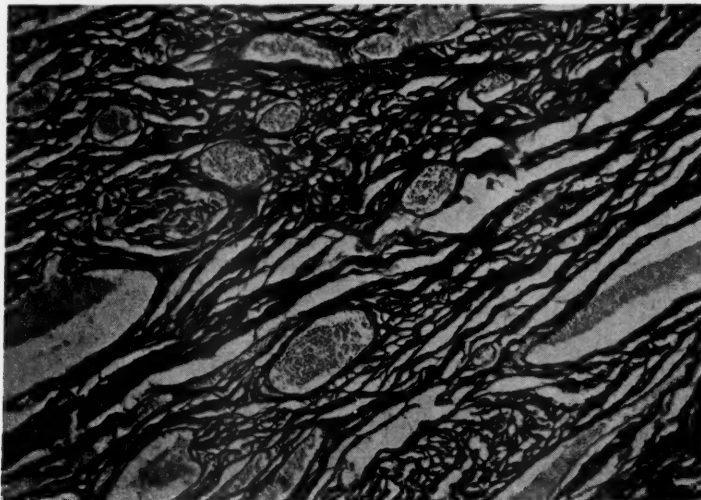


Fig. 9.—Cervix from Fig. 8 showing increased vascularity and connective tissue entirely prominent.

the same cervix, but also its level with respect to the external os may vary as much as 6 or 8 mm. In these specimens there was no definite correlation of the patient's age, parity, and the local cervical lesion with the nature of the fibromuscular junction. In general, the transition was less gradual in the more normal specimens. Five uteri were obtained from nulliparous women of child-

bearing age. The cervixes were quite normal, the fundamental tissue was fibrous, the smooth muscle was sparse and widely scattered, and the fibromuscular junction abrupt.

.....
"II. *The Pregnant Uterus.*—

"A. *Intrinsic structure of cervix and isthmus during early pregnancy:* Specific estimates of hypertrophy and hyperplasia of the muscle and fibrous tissue elements are not possible with the techniques which have been employed here.

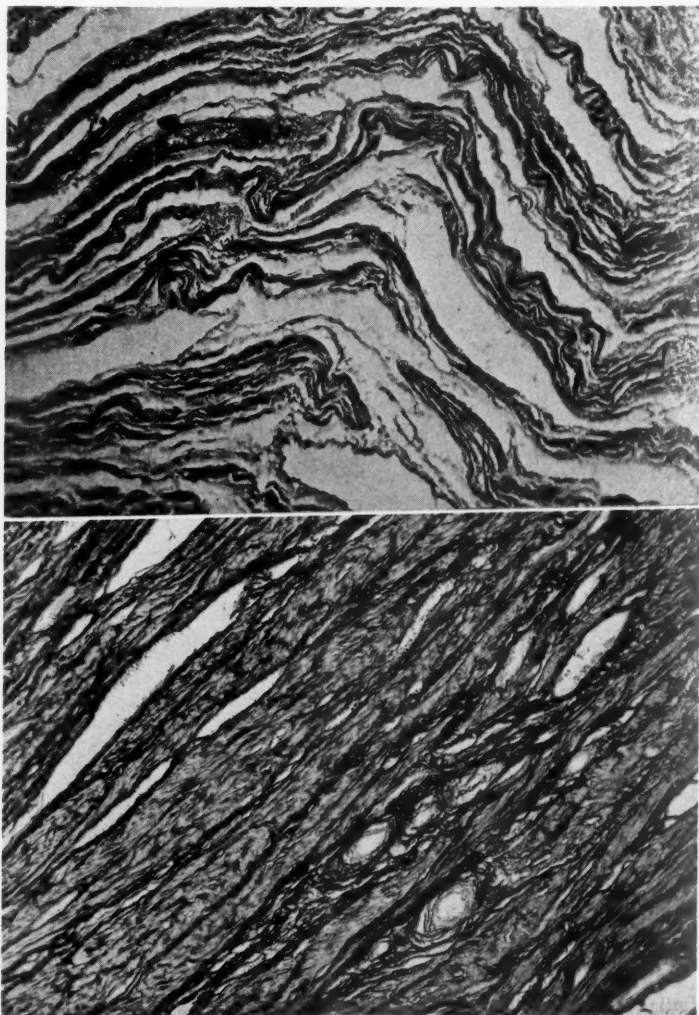


Fig. 10.—Lower uterine segment of same specimen showing slight transition to muscular structure.

Fig. 11.—Higher up showing transition through predominance in muscular structure.

There is the distinct impression of the enlargement of both of these elements and of an increase in their number. Also, the presence of edema in the pregnant specimens is quite definite.

"By the means which have been used, it is not possible to confirm the reported changes in elastic tissue during pregnancy. Elastic fibers are present in the same (negligible) quantity as in the nonpregnant specimens, and with the

same haphazard arrangement except with reference to the blood vessels. Elastic stains were available in the corpus in only two of the pregnant specimens. In these the fibers were limited to the outer third of the uterine wall, being interspersed among the fibrous connective tissue which separates the muscle bundles. They were considerably more numerous in the tissue immediately above the cervix.

"With the exceptions of greatly increased vascularity and edema, the fundamental structure of the cervix was found to be similar to that of the nonpregnant specimens. The basic tissue is fibrous. Varying quantities of smooth muscle are present, amounting to from 2 to 40 per cent, with an average of about 10 per cent. The distribution of muscle is likewise variable, though the presence of small bundles in the central portions of the tissue is somewhat more common. When they do appear, the bundles are heavily interspersed with fibrous tissue, and appear to have insignificant sphincteric possibilities."

Our study consisting of nineteen uteri; two infantile uteri (one at 14 years of age), three pregnant uteri (one at 12 weeks, one at 20 weeks, one at 26 to 28 weeks), the remaining material was selected at random. The results from this study coincide entirely with the more extensive work of Danforth in practically every detail, as our illustrations will clearly bring out. In our presentation, we use colored slides, but in publication we shall use black and white illustrations with proper explanation.

In studying this material we used hematoxylin-eosin, Van Gieson's stain, Masson's stain, and orcein. Stains as follows:

Masson Stain

Solution A	
Acid fuchsin	0.6 Gm.
Ponceau De Xylidine	1.4 Gm.
Distilled H ₂ O	205 c.c.
Acetic acid (glacial)	2 c.c.

Solution B	
Phosphatungstic acid	2 Gm.
Distilled H ₂ O	200 c.c.

Solution C	
Acetic acid (glacial)	4 c.c.
Distilled H ₂ O	200 c.c.
Light green 1 per cent	1 Gm.

Orcein Stain

Orcein	1 Gm.
Absolute alcohol	100 c.c.
Hydrochloric	1 c.c.

Van Gieson Stain

1 per cent stock solution picro fuchsin	1 Gm.
Acid fuchsin	5 c.c.
Saturated solution picric acid	100 c.c.

We used these stains separately, and particularly Orcein for elastic tissue, knowing well from previous experience that elastic tissue played a most minor part in the bulk of uterine structure.

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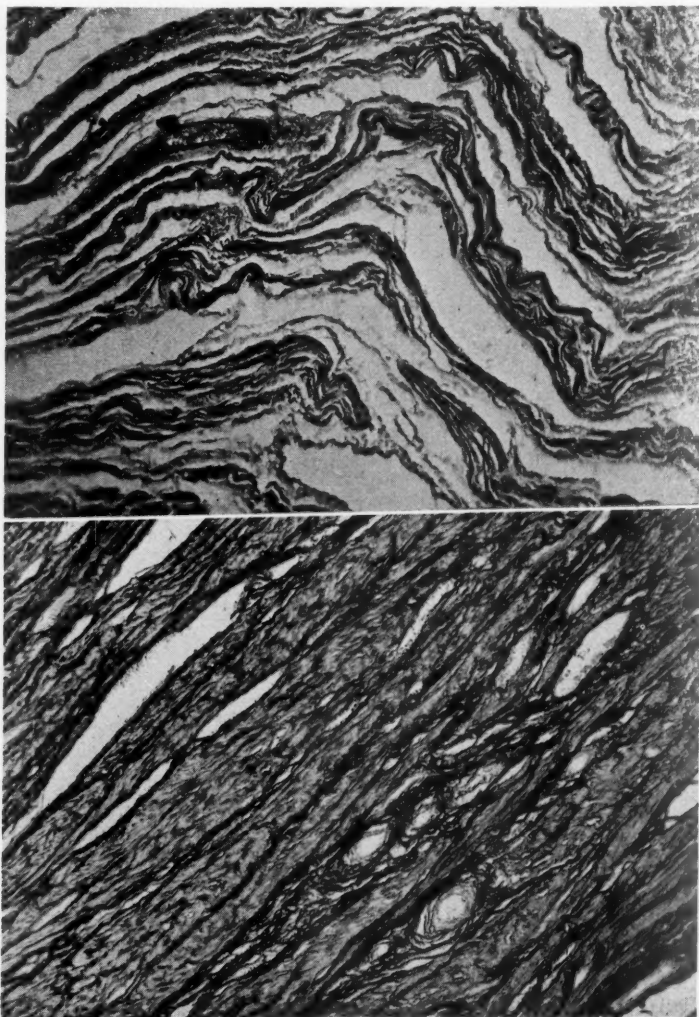


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We used these stains separately, and particularly Orcein for elastic tissue, knowing well from previous experience that elastic tissue played a most minor part in the bulk of uterine structure.

We have included only a few case histories of outstanding cases of functional rigidity as the whole subject revolves on Danforth's new findings. We had planned originally to go into detail concerning uterine innervation and the effects of endocrine reaction as regards the softening of the lower uterine segment and cervix. There is no doubt that there may be several contributed factors, but essentially it must now be considered that the fundamental fibrous nature of the cervix plays the most important part.



Fig. 12.—Gross specimen twenty-eight weeks pregnant showing complete cervical canal and development of lower uterine segment.

For the following we are indebted to Dr. M. A. Roblee of St. Louis, who has a wide experience in this field.

“Conization of the Cervix.—

“It is difficult to evaluate cervical dystocia and trauma to the cervix at childbirth in the previously coned cervix. Most patients that have had conizations are multiparous and are not desirous of more children as a rule. Their average age would be past the mid thirties. We have averaged approximately 100 conizations a year, and out of this number in the past sixteen years we had approximately 150 observed pregnancies in women who had had conization of the cervix. Surprisingly little trouble has developed. In a study of cervical dystocia and Dührssen incisions of the cervix, no references were made to previously coned cervixes as being a possible factor.

“Although we practice and teach that conization should not be performed during the active childbearing age, there is little clinical evidence in our hands to support this conclusion. One reason for this is undoubtedly the technique of not re-entering the cervical canal after the original cone has been removed. A different electrode designed solely to undercut the hypertrophied cervical lips without burning again the endocervical portion of the cervix reduces the glandbearing area of the cervix without damaging the fibrinous muscular junction of the cervix as described by Danforth in a recent article. Danforth points out that as pregnancy develops, the cervix becomes the lower portion

of the uterus and the muscular fibrinous elements contribute to effacement and dilation of the cervix.

"Of the approximately 150 cases of observed pregnancy following conization, ten might be classified as having varying degrees of cervical dystocia, however, none required incisions. Dilation progressed surprisingly rapidly although from four to six hours of labor were required to thin out and obliterate the cervical canal before dilation occurred. Eight cases received manual dilatation of the cervix after effacement.

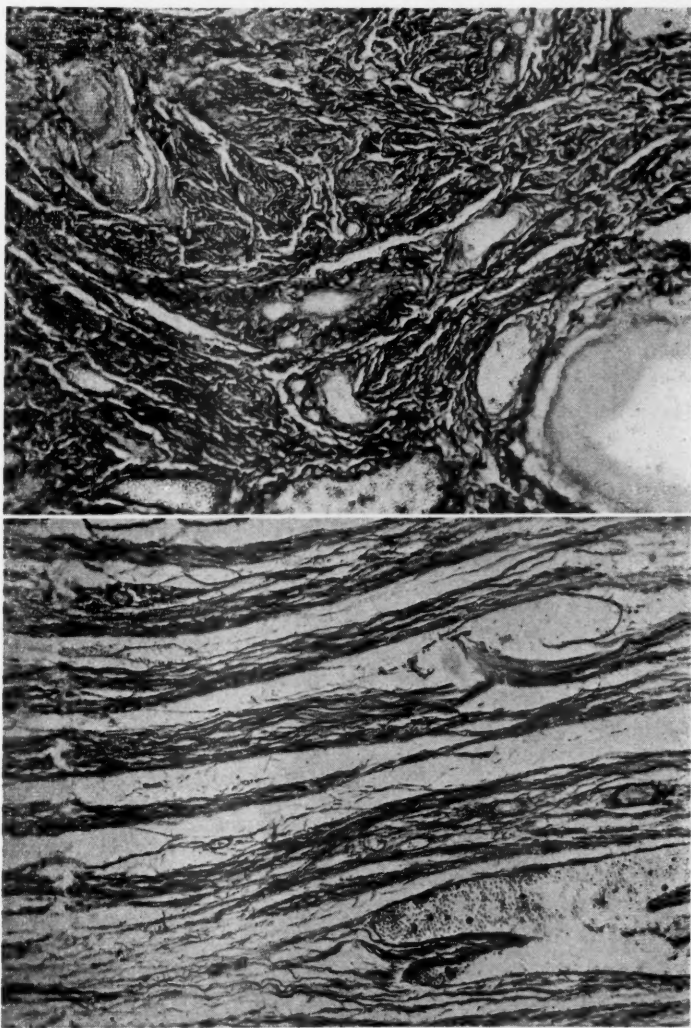


Fig. 13.—Cervix low down from Fig. 12 showing pregnancy entirely connective tissue.

Fig. 14.—Taken high up from Fig. 12 showing a mixture of muscle tissue to fibrous tissue—about 50-50.

"In regard to fertility after conization, it has been observed that when the chronic endocervicitis is cleared up by a subtotal removal of the gland-bearing area which permits a normal cervical secretion to follow conization, conception readily occurs (in the absence of other lesions) and none of these cases acquired cervical dystocia."

We also realized fully that the innervation of the uterus may play a part in action concerning the dilatation of the cervix, but as knowledge of uterine innervation has not as yet been cleared, especially as it concerns the motor nerves very little can be said emphatically. However, Masters of our service has given this subject much study in connection with work on caudal anesthesia, and we are indebted to him for the following:

"The question of uterine nerve supply is one of the major unsolved problems in the field of gynecological anatomy. The entire subject is surrounded by conjecture based on a minimal amount of factual information.



Fig. 15.—The uterus of a 14-year-old girl showing vagina, cervix, isthmus, and body.

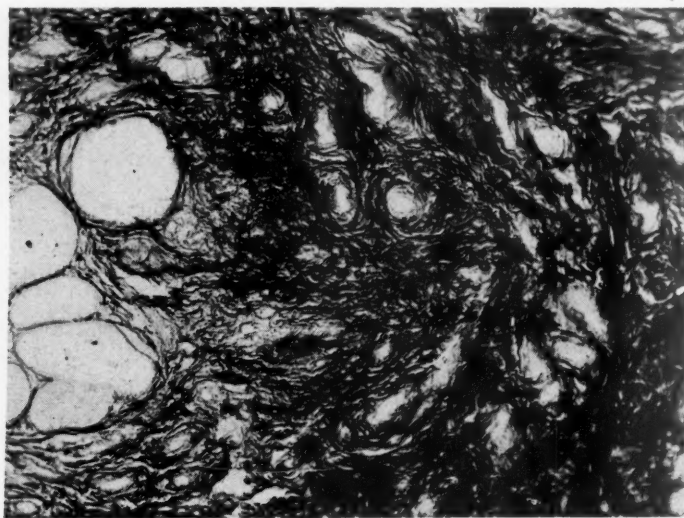


Fig. 16.—From cervix showing pregnancy, entirely connective tissue.

"As the result of the pioneer work of Cleland, we know something of the sensory component of the uterine nerve supply, but the motor innervation of the uterus is, as yet, unresolved.

"The basic nerve supply to the uterus is through the autonomic system as perhaps best demonstrated by the opposing Kuffer forces of the sympathetic and parasympathetic systems supply the uterus with both afferent and efferent nerve fibers. The sensory fibers run through the ganglions of the eleventh and twelfth thoracic segments to synapse through the dorsal root ganglions of those levels. The motor inertia is as previously stated, unsolved. A theory

based on clinical observations of DeLee places the origin of the motor supply to the fundus above the level of the tenth thoracic vertebra and presumes a downward pathway for motor fibers through the aortic plexus to the ganglion of Frankenhauser. Further nerve supply of questionable motor component is believed to arise from a combined sympathetic and parasympathetic source.

Fig. 17.

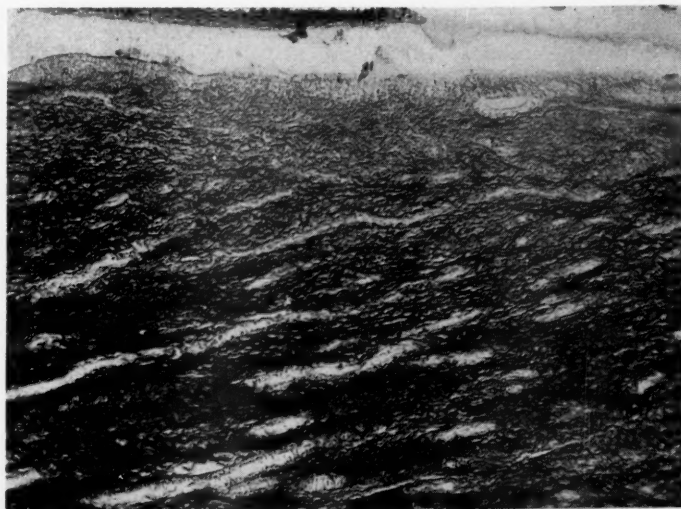


Fig. 18.

Fig. 17.—From isthmus showing a mixture, but connective tissue is still most prominent.

Fig. 18.—From Fig. 15 from body of uterus showing prominence of muscle structure in that region.

As stated above the sympathetic component is of unknown origin and the parasympathetic plexus arises from the second, third, and fourth sacral nerves. This innervation is believed to control the lower uterine segment and cervix. Visceral efferent fibers believed to be motor to the longitudinal muscle fibers of the lower uterine segment and to the circular muscle fibers of the cervix have origin in the sacral parasympathetic plexus.

“Actual clinical experience both in following closely the progress of labor, and the definitive use of caudal analgesia have failed to answer the question of

motor innervation and, of course, have widely substantiated the source of the sensory component of the uterine nerve supply.

"Experience in St. Louis Maternity Hospital based on better than fifteen hundred caudal analgesia attempts have certainly overwhelmingly verified the source of sensory innervation of the uterus to include the eleventh thoracic nerve root as its highest component."

Caudal analgesia levels taken as high as the fourth or sixth thoracic nerve roots have frequently slowed or even stopped labors, particularly when initiated early in the first stage of labor. This clinical observation would tend to lend credence to the assumption that the motor innervation to the fundus takes its origin (in part) from sources higher than the tenth thoracic nerve root. However, while the clinical observation of slowing first stage 1 of labor with high caudal analgesia levels is undoubtedly well founded, the same type slowing or stoppage of labor with a heavy twilight early in the first stage 1 has also been frequently noted, though to a lesser degree.

We do not agree with Hingran and his co-workers in the belief that controlled caudal analgesia levels shortens stage 1 labors. In theory this reduction in the length of time necessitated by stage 1 labors should occur, because a level sufficient to control the distress of contractions (T-11) would of necessity have inactivated the theoretical parasympathetic motor component to the lower uterine segment and cervix (S2-S4). We have seen no real over-all induction in stage 1 labors. As a matter of fact, it is our opinion that stage 1 labors are moderately prolonged under caudal analgesia.

Also the question of what part the ovarian hormones play in the softening of the cervix is not fully understood but there can be no question that they must play a part, especially progesterone. In face of functional rigidity in the cervix, it is quite possible that their unbalance, or the deficiency of one or the other or possibly both may play a part, especially in cases of rigidity in the elderly primipara due to the much later date that these cases first receive this softening.

Conclusions

1. Functional rigidity of cervix in the elderly primipara is due to its fibrous nature, having not been previously stimulated by the effects of previous hormone physiology.
2. Annular cervical detachment takes place at the fibromuscular junction, as determined by the study of tissue from two such cases.
3. Amputation of the cervix leads to premature labor. Andebert and Pinard quote twenty-four cases of pregnancy in cases of this type in sixteen women, only five going to term. Obviously with the fibrous cervix removed, there was no structure to keep the uterus from dilating.
4. The cervix after conization, as quoted from Dr. Roblee in over 1,500 conization cases, who states that pregnancy occurred in 10 per cent, only eight cases in 150 gave any cervical difficulty, only a little manipulation, no incisions or sections.

We wish to express our thanks and deep appreciation to Miss Geraldine Brennan for her staining of the specimens, and to Mr. K. Cramer Lewis for his development of the colored photomicrographs which entirely helped to make this contribution.

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Discussion

DR. M. PIERCE RUCKER, Richmond, Va.—Dr. Danforth, by his study of frozen sections of the monkey's uterus in various stages of labor, has already caused me to change my ways in the management of the third stage of labor. I was in hope that he and Dr. Schwarz would explain to me in words of one syllable why some cervixes, with presumably the same structure, dilate and some do not.

Sackett, in a paper that he read before the Richmond Academy of Medicine several years ago, defined cervical dystocia as the failure of the cervix to dilate or to be effaced, (when there is no obvious mechanical reason therefor), within a reasonable time despite frequent and forceful contractions of the uterus. He reported 86 cases, a frequency of 1.05 per cent. Under etiology he says that those who admit the existence of cervical dystocia offer two general explanations of its origin. The first points to a constitutional deficiency, manifested by obesity, lack of feminine habitus, endocrine dyscrasia, disturbance of menstruation and fertility, and maldevelopment of the genital tract.

The second theory stresses rigidity and stenosis of the cervix as a result of fibrosis following operative or obstetric trauma, abortions and infections.

From the work presented today it would seem that the cervix has normally enough fibrous tissue to prevent its dilatation, if fibrous tissue were the answer. Why any cervix dilates is the important question. All of us have seen, I am sure, cervixes destroyed by radium and the normal structures replaced by dense fibrous tissue. I recall one such case in which the entire vaginal vault was a mass of scar tissue with merely a little depression to represent the cervix. This patient had a precipitous labor a week before the time set for her cesarean section.

I am convinced that a great number of cervixes do not dilate because of a constriction ring which firmly fixes the baby to the body of the uterus. In my experience, this occurs in about once in 90 cases. I have not been impressed that a rigid cervix has been a factor except in the very exceptional case. I have resorted to Dührssen's incision once in the past twenty years.

The work of Drs. Schwarz and Woolf explain why, immediately after delivery, the cervix hangs like a loose crinkled cuff with no evidence of contractility. It does not show why it dilates during normal delivery and fails to dilate in cervical dystocia.

DR. KARL MARTZLOFF, Portland, Oregon.—Dr. Schwarz' slides are beautiful and disturbing, because they upset one's previous ideas concerning the mesodermal structure of the cervix. Tonight Dr. Schwarz confirms Dr. Danforth's recently published observations.

I would like to ask whether Dr. Schwarz has been able to prove that the cervix possesses an external longitudinal layer of musculature as described by Stieve; also whether his observations confirm those of Dührssen, who I believe described an outer layer of connective tissue? I would also like to ask what method of fixation was used on his material; if his material is old; whether the age of the material and the fixation fluid would have any effect on the differential staining? These questions arise, because in otherwise fibrous areas, Dr. Schwarz' slides show clearly the musculature of the blood vessels. It occurred to me that the vascular musculature might possibly retain this differential staining property while musculature otherwise situated might not. Using maceration methods, I have never been able to dissect out any tissue layers in the cervix except right at the place where the portio attaches to the

vaginal vault. There one can, in not too abnormal uteri, hit a fairly good superficial cleavage plane which can be followed for about one centimeter.

DR. SCHWARZ (Closing).—In answer to Dr. Rucker's question about the constriction ring and why one cervix will dilate and another will not, I think the knowledge on that point is rather vague, but there can be little doubt that it must be due to estrogenic stimulation plus progesterone. Now whether this stimulation is adequate or due to the normal stimulation of a rather toughened cervix, of course no one can say.

So far as rings of musculature in the cervix are concerned, Dr. Danforth has proved them nonexistent. I could not find any signs of encircling musculature. The cervical muscle is of an infiltrating type. It comes on the outer third of the uterus a little earlier but for no appreciable depth. On the other hand, there is an admixture of the substances and there can be no question about the softening of the isthmus during pregnancy which produces a Hegar's sign. The very fact that this occurs would indicate to me that the reason the cervix does not soften along with the isthmus is because of this fact.

Another point I wanted to make is the fact that formerly the so-called amputation of the cervix was done very frequently. I have seen two cases where the patient carried the pregnancy to the fourth, fifth, or sixth month, and then went into labor. Twenty-four cases have been reported by others and in only five instances did the patient go to term. The explanation of that is now simple to me, for they merely cut away the fibrous tissue and there was nothing to hold the pregnancy in.

THE EXPECTANT MANAGEMENT OF PLACENTA PREVIA*

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THE maternal mortality in placenta previa has been appreciably reduced in the past decade mainly by the replacement of blood loss by adequate transfusions of whole blood. On the other hand, fetal mortality remains high, due in great measure to prematurity. In order to improve the fetal results, it is necessary to carry these patients closer to term. Ample, properly matched blood, and caution in the use of vaginal manipulations may make it possible to continue the pregnancy until the child is larger, and so increase the fetal salvage. Recent reports by Macafee¹ and Johnson² have suggested this possibility and have cast doubt upon the correctness of the dictum that there is no expectant treatment of placenta previa.

In the present report we wish to present the results in 105 cases of placenta previa seen at the University of Virginia Hospital during the past eleven years. Forty-one of these patients were treated in an expectant manner. Obviously, there can be no expectant treatment once labor has begun. Likewise, if the patient is at or near term, there is no advantage in attempting to prolong the pregnancy.

Of the 105 cases of placenta previa twenty-one were classified as central, twenty-three as partial, and sixty-one as marginal.

TABLE I. TYPE OF PREVIA

Central	21
Partial	23
Marginal	61
Total	105

TABLE II. METHOD OF TREATMENT AND DELIVERY

METHOD	NO.	PER CENT
Cesarean section	44	42
Rupture of membranes	32	30
Scalp traction after rupture of membranes	2	2
Spontaneous onset of labor and vaginal delivery	20	19
Version	7	7
Total	105	100

The most common method of treatment for delivery was cesarean section (42 per cent), with the operations divided equally between the classical and low cervical types, twenty-two of each. All cases of central previa were delivered

*Read (by invitation) at the Seventieth Annual Meeting of the American Gynecological Society, at the Seignior Club, Montebello, Quebec, June 17 to 19, 1947.

†Dr. Williams died August 19, 1947. Proof corrected by Dr. W. N. Thornton, Jr.

by cesarean section. Simple rupture of the membranes was the common alternative method of treatment to cesarean section, and was done in thirty-two cases (30 per cent). In two instances scalp traction was applied after rupturing the membranes. In twenty patients the onset of labor was spontaneous with spontaneous vaginal delivery. All of these were of the marginal variety except one which was classified as partial. Those treated by version were admitted in labor with dead or nonviable infants, in two of whom the children were presenting transversely. In these cases a foot was brought down into the vagina, and full cervical dilatation awaited before completing the delivery. This was a method employed to empty the uterus of patients in labor with dead or non-viable children, and was not a procedure of choice in the selective management of placenta previa.

Diagnosis

The diagnosis was established by determining the location of the placenta either at the time of cesarean section or on vaginal examination. An attempt at diagnosis by various methods of x-ray examination was made in sixty-four of these patients. In fifty-one the x-ray diagnosis was positive for placenta previa, while in thirteen the x-ray findings were inconclusive.

Maternal Mortality

There was one maternal death in the one hundred and five cases (0.95 per cent). This was a multipara admitted to the hospital in her eighth month of pregnancy with a dead fetus. There had been persistent bleeding at home for three weeks, during which time her local physician had made numerous vaginal examinations, following one of which an alarming hemorrhage occurred. The patient was then sent to the hospital. At the time of admission she was almost exsanguinated and had a temperature of 101° F. After reacting following transfusions, a vaginal examination was done and revealed a partial previa. The membranes were ruptured artificially and an easy vaginal delivery followed. The patient died on the fifth postpartum day of a generalized infection, which was confirmed by postmortem examination. This death occurred before the era of chemotherapy or antibiotics. This is obviously a preventable death, due to the error of performing repeated vaginal examinations in the home in a case of antepartum bleeding, and for failure to replace blood loss or to send the patient to a hospital promptly, where appropriate management could have been instituted.

Fetal Mortality

Twenty-nine children of these one hundred five patients did not survive. Fourteen were stillborn and fifteen died neonatally, a fetal mortality of 28 per cent. Of the seventy-four patients who were either successfully carried to term or who did not have their initial bleeding until the child was of term size, eight babies (10 per cent) were lost. On the other hand, of the thirty-one patients who either went into labor spontaneously or in whom the pregnancy was terminated before the child attained a size of 2,500 Gm., twenty-one babies (68 per cent) were lost.

Seven patients went into spontaneous labor prematurely, and of these seven premature babies, five died neonatally. Thus, even though an expectant attitude may be adopted, some of these patients will go into spontaneous premature labor with its adverse effects on the fetal results.

TABLE III. FETAL RESULTS

METHOD	NO.	TERM 74			PREMATURE 31		
		LIVED	DIED		LIVED	DIED	
			STILL- BORN	NEONA- TALLY		STILL- BORN	NEONA- TALLY
Spontaneous	20	12	1	0	2	0	5
R. of M.*	34	22	4	1	4	2	1
Cesarean	44	32	0	1	4	0	7
Version	7	0	1	0	0	6	0
Total	105	66	6	2	10	8	13
		8 or 10%			21 or 68%		
Total Fetal Deaths 29 or 28%							

*Rupture of membranes with two cases with scalp traction.

The recent reports in the literature show similarity of results in placenta previa. Some of these are shown in Table IV. The maternal mortality averages

TABLE IV. RECENTLY REPORTED RESULTS IN PLACENTA PREVIA

AUTHOR	NO. OF CASES	MATERNAL DEATHS		FETAL DEATHS*	
		NUMBER	PER CENT	NUMBER	PER CENT
Macafee ¹	174	1	0.57	41	23.0
Davis & Campbell ³	325	2	0.6	104	31.6
Yepes & Eastman ⁴	111	1	0.9	52	46.8
Williamson & Greeley ⁵	162	5	3.1	50	31.1
Seeley ⁶	250	7	2.8	91	34.6
Johnson ²	79		0.0	26	31.0
Scott ⁷	191	5	2.6	56	29.6
Totals	1,292	21	(1.6)	420	(32.5)

*No correction.

1.6 per cent, whereas the fetal loss is 32.5 per cent, or approximately one out of three babies is lost. The earlier methods of treatment resulted in 5 to 10 per cent maternal deaths and about 40 to 60 per cent fetal deaths.

Treatment

The first essential in the treatment of antepartum bleeding is the determination of the blood type and Rh factor. Ample properly matched blood should be available and should be given in adequate quantities, dependent on the amount of blood loss and the condition of the patient.

Placenta previa requires hospitalization for diagnosis and treatment. Attempts to determine the cause of antepartum bleeding by performing vaginal examinations in the home do not improve the outlook for the mother or her baby. Pelvic examinations may cause more hemorrhage by separating additional areas of the placenta. Occasionally, these examinations seem to start uterine contractions, so that some definitive type of treatment must be employed because of the presence of labor, even though the condition of the patient may still be

poor and the child too small to survive. In addition, vaginal examinations, particularly if packing is placed in the vagina and around the cervix, carry the added risk of infection, as is evidenced by our one fatality.

Helpful information in diagnosis may be obtained by abdominal examination. Usually the presenting part does not engage satisfactorily in the superior strait of the pelvis, if any appreciable degree of placenta previa is present. The high unengaged presenting part or an abnormal presentation, such as transverse or oblique, in the presence of antepartum bleeding, is strongly suggestive of placenta previa. An attempt at diagnosis by some method of x-ray examination may be undertaken if the condition of the patient permits.

If the patient is at term or has an apparently viable baby, a method of delivery may be selected as soon as the general condition of the patient permits. If the presenting part is not engaging in the pelvis, vaginal examination is apt to be particularly hazardous. In such instances we often omit vaginal examinations, and when delivery is decided upon, if the presenting part is still floating above the pelvic inlet or presenting abnormally, we deliver the patient by cesarean section. It is possible that the occasional patient treated in this manner may have a premature separation of a normally situated placenta, or some uncommon condition, which may have caused the bleeding. We believe, however, that an abnormal presentation with a viable baby is more safely delivered by cesarean section, so, while the preoperative diagnosis may at times be incorrect, it is felt that the patient received the wisest treatment.

If the presenting part is dipping into the pelvis and delivery has been decided upon, a vaginal examination is done. The condition of the cervix is gently determined, and the lower segment lateral to the cervix is palpated. When the presenting part cannot be readily felt through the tissues lateral to the cervix, it suggests the presence of placental tissue in the lower segment. If the cervical canal is short and admits the finger, the region around the internal os is cautiously felt. In the event placental tissue is palpated, every effort is made to avoid disturbing its attachments. If the cervix is short, soft, and patulous, and a portion of the internal os is not covered by the placenta, the membranes are ruptured. When the cervix is not favorable for vaginal delivery, or if the internal os is completely covered by placental tissue, delivery is then accomplished through the abdomen.

In the event that the child seems too small to survive, and if labor has not begun, an expectant attitude may be adopted. A gentle examination and inspection of the vagina and cervix may be done to eliminate the possibility of some infrequent cause of bleeding such as ruptured varices, or cervical tumors, but the cervical canal should not be explored. These patients should be kept under observation, preferably in the hospital, although we have permitted some of them to return home, with instructions to abstain from sexual intercourse, to permit no vaginal examinations, and to return to the hospital with the first recurrence of bleeding. Forty-one of our patients were kept under observation for periods of time varying from two days to three months in an effort to obtain a child which would survive. Fourteen of these patients had two or more periods of hospitalization for recurrent episodes of bleeding. Of these forty-one patients,

five babies (12 per cent) were lost. One was a term baby delivered by cesarean section which died neonatally of congenital malformations, and four were prematures, of which one was stillborn and three died neonatally. The fetal mortality of 12 per cent in this group treated expectantly is considerably better than the fetal mortality of 28 per cent for the entire series. In view of the better fetal results and with no apparent increased maternal risk, it would seem that an expectant attitude in the management of placenta previa is worthy of trial.

TABLE V. FETAL RESULTS WITH EXPECTANT TREATMENT

METHOD	NO.	TERM 32		PREMATURE 9	
		LIVED	DIED	LIVED	DIED
Spontaneous	11	9	0	1	1
Rupture of membranes	15	10	0	3	2
Cesarean	15	12	1	1	1
Totals	41	31	1 (3%)	5	4 (44%)

Total Fetal Deaths 5, or 12 per cent

Summary

One hundred five cases of placenta previa with one maternal death (0.95 per cent) and twenty-nine fetal deaths (28 per cent) are reviewed. The adequate replacement of blood loss, and caution in the use of vaginal manipulations, with delivery either by cesarean section, or induction of labor by rupture of the membranes, dependent upon the station of the presenting part, the degree of previa, and the condition of the cervix, have improved the maternal results in placenta previa. An improvement in the fetal results is dependent upon an attempt to carry these patients closer to term. Of seventy-four babies weighing 2,500 Gm. or more, eight (10 per cent) were lost, while on the other hand, of thirty-one babies weighing less than 2,500 Gm., twenty-one (68 per cent) were lost. An attempt to carry patients with placenta previa to term seems to be reasonably safe and is worthy of trial, although some of them will go into spontaneous labor prematurely, while others will have such persistent or profuse bleeding that one is reluctant to continue an expectant attitude. In forty-one patients so managed, there were five fetal deaths (12 per cent), four prematures, and one term baby which died of congenital defects.

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Discussion

DR. ROBERT KIMBROUGH, JR., Philadelphia, Pa.—Dr. Williams is to be congratulated on the excellent results which he has obtained in the treatment of this series of cases of placenta previa, not only because of his low and unavoidable maternal mortality, but particularly because of the low fetal death rate. I am sorry that Dr. Williams did not have sufficient time to present a table in which he has summarized recent papers on this subject

from England and this country. These studies show that the maternal death rate by the use of copious transfusions, and antibiotics and sulfonamides has been reduced to approximately 2 per cent. The major problem is that of a high fetal mortality which in his collected series is somewhat over 30 per cent. In the forty cases in which Dr. Williams was able to use the expectant treatment and thereby bring these babies closer to full term, his mortality rate was under 12 per cent, and in this group not one mother was lost. These amazingly good results attest the soundness of his procedure. Too often the obstetrician in his anxiety for the welfare of the mother is prone to disregard the rights of the child to a better chance of survival. I must confess, however, that I am in diametric disagreement with Dr. Williams in allowing patients who have had one or more hemorrhages from placenta previa to leave the hospital before delivery. Even though the patient is in the hospital, an alarming amount of blood can be lost before adequate measures can be taken for transfusion and for control of hemorrhage.

DR. WILLIAM C. DANFORTH, Evanston, Ill.—Some fifty years ago Jaggard, the predecessor of DeLee at Northwestern, enunciated the doctrine that "there is no expectant treatment for placenta previa." The increase in hospitals for the care of parturient women and the experience of obstetricians has modified this dictum to some extent, although still, in most cases, immediate and decisive therapy is called for.

As to the active treatment of placenta previa, I agree with the essayist almost completely. His recommendation that all preparation for restoration of blood loss be made in advance is sound doctrine. A Wassermann or Kahn, the determination of the Rh factor, cell volume, blood typing, and crossmatching should all be done at once on the admission of the patient to the hospital. If the patient has been seen before, the Kahn and the Rh should be known already. That vaginal examination should not be made until all is ready to proceed with the chosen method of delivery is commonly accepted.

Recent papers, as that of Watson and Gusberg, and of Davis and Campbell, incline toward a choice between cesarean section and rupture of the bag of waters, with or without scalp traction by means of the Willett forceps or similar instrument. With this attitude the essayist agrees. The great majority of cases may be managed by one or the other of these two, and the avoidance of the introduction of a foreign body is wise. That the bag is not as yet completely discarded by all clinics is evidenced by the paper of Dr. Seeley before this Society two years ago in which he reported 250 cases of placenta previa in 105 of which the bag had been used. There may still be a place for the bag in an occasional case, but its place is definitely far less than formerly. The vaginal pack I would reject completely: first, because so far as my experience has shown it is inefficient, and, second, because it is dangerous from the standpoint of infection. Such patients as I have seen who have entered the hospital after packing by a physician at home have not caused me to have any confidence in this method.

As to the method of cesarean section, the essayist employs both the classical and the low cervical technique. I believe the latter is definitely the better, and use it in all cases in which abdominal delivery is chosen. I believe it has two advantages. First, should packing be needed, it is far more easily introduced in the lower type of operation; and, second, should there be bleeding from open sinuses in the lower uterine segment, hemostasis by means of actual suture may be employed. This has served me well in a number of instances. In our own work, of the last 45 cases of placenta previa, 21 were delivered by cesarean section. In the entire number there was no maternal death.

Now as to the question of expectancy, I believe that, should the baby be smaller than is compatible with probable continued life after delivery, one may defer interference or await the possible advent of normal labor under advantageous circumstances. By advantageous circumstances I mean that the patient is in a hospital in which there is a well-equipped obstetric service with someone at hand all the time who is able to interfere at once should it be needed. It seems to me that the essayist is extremely bold in allowing these women to go home with instructions to return should repeated bleeding occur. It is true that, as in ectopic pregnancy, few women die from the first bleeding. But no one knows what the second

hemorrhage may bring, and the fact that one has already taken place means that some unfolding of the lower uterine segment has occurred, and this only increases as time goes on. I believe that expectancy should only be practiced with the patient in a hospital which is so staffed and organized that immediate interference may be begun by a trained individual on the appearance of hemorrhage. I agree with the statement of Adair, made in the discussion of Seeley's paper, "Expectancy or delay is extremely hazardous and if generally adopted would lead to an increased mortality. It should not be carried out except in a special hospital and under expert care." Macafee of Belfast, who is quoted by the essayist, says, "If placenta previa is suspected it is not necessary to keep the patient in a hospital provided she is within a short distance of it." However, he states that this does not apply to multiparas. As these make up the majority of the patients who have placenta previa, his statement is robbed of much of its force.

DR. JOSEPH L. BAER, Chicago, Ill.—At the risk of redundancy I beg to quote a Fellow of this Society, N. Sproat Heaney, to the effect that more patients with ectopic pregnancy die in the hospital while under observation than do those who are treated outside of the hospital. The same applies to placenta previa. Those who are kept under observation indefinitely can eventually sustain major hemorrhage, and before their needs can be met they may sustain exsanguination to the degree that they reach irreversible shock and succumb. I am firmly of the opinion that patients with a diagnosis of placenta previa should not be kept under prolonged observation, but that their pregnancies should be terminated irrespective of the estimated age of the fetus involved.

Concerning the method of termination, I beg to offer a comment concerning rupture of the membranes. Successful rupture of the membranes in the many decades past was confirmed by the demonstration of hair from the scalp of the fetus, and the rupture of the membranes was considered consummated. That, in itself, is totally inadequate for the purpose. It should include drainage of the liquor amnii in order to allow the uterus to contract, and thus to initiate active labor. And so I think it behooves us whenever we speak of rupture of the membranes as a therapeutic procedure in the treatment of marginal placenta previa or for the induction of labor to speak of "rupture and drainage."

DR. SUBODH MITRA, Calcutta, India.—I agree with Dr. Williams' outline of treatment that means no immediate termination of the pregnancy.

I have had a patient near term who had hemorrhaged the day before. There was no bleeding when I saw her so I kept her under observation. In the course of a week's time she had a normal delivery. That case gave me the idea that we should not always follow the beaten track of no temporization in placenta previa. If properly taken care of by hospitalization, we give the patient a better chance to go a little further. Later I treated a number of cases—not all of a serious type—in which I followed that expectant procedure and got good results. So I think it is high time for us to think seriously about whether we should teach this method of expectant management to our students. I think, however, it should not be taught to the students in general.

These patients should never be sent home. In the management of these cases by cesarean section, I have my own way of coming to a decision. It is difficult to know whether it is a case of central or lateral placenta previa unless one makes a thorough examination. I first determine whether the cervix is tubular and undilated, and in that case I advise cesarean section, and that is the only time I do a cesarean section. Otherwise, if the cervix is found taken up and dilatable, one must seriously consider whether it is a case for cesarean section or not.

DR. SAMUEL A. COSGROVE, Jersey City, N. J.—I think perhaps some of the extent to which Dr. Williams has been misunderstood in his purpose in presenting his cases tonight is due to the unfortunate title. Had he called his paper a plea for expectancy in a few selected cases of placenta previa, the reaction to what he has said would have been more generally favorable.

The number of premature cases in his series, of 20 odd, is approximately 25 per cent. If you deduct those who went spontaneously into labor, there were only relatively few cases to which his proposal to tide the patients over would be applicable. Certainly that possibility must not be overlooked or forgotten. All of us, I am sure, have had specific instances in which that possibility has been exploited with the happiest results. And it is only in that sense, I think, that Dr. Williams is presenting to us a plea for expectancy.

DR. ARTHUR H. BILL, Cleveland, Ohio.—I do not expect to discuss the general treatment of placenta previa, but I think the main point in his paper is that of expectant treatment. I have had some good results from expectant treatment and have saved some babies, and evidently he has also. It is rather characteristic of placenta previa that there will be one hemorrhage, this will stop, and then there will be a recurrence because, as it has been described, the case is one of unavoidable hemorrhage.

I agree with the discussants that if we carry out the expectant treatment we should insist on the patient being in bed and in the hospital during this period of observation. Many years ago there was a patient in the Cleveland City Hospital who had had a moderate hemorrhage, and after a week of no bleeding insisted upon going home because nothing was being done for her. When all arguments had failed, she was permitted to be taken home after signing a release, which absolved the hospital from blame, but did not help the patient. Some days later she was brought back to the hospital in an ambulance with a tremendous hemorrhage, and died in the admitting room before anything could be done for her. If she had remained in the hospital she probably could have been saved. I always insisted, thereafter, that in any case of placenta previa, if the expectant treatment is carried out, the patient should be kept in the hospital and under observation. There are cases where good results may be obtained in this way.

As to the ultimate delivery, prophylactic blood transfusion and classical cesarean section are in order. I prefer classical section because my policy is to keep the uterine incision away from the placental site, for if this is done there will be no post partum bleeding from that source.

DR. WILLIAMS (Closing).—The table which Dr. Kimbrough mentioned was simply a total of the recently reported cases of placenta previa, 1,292 cases with 21 maternal deaths, an average maternal mortality of 1.6 per cent. There were 420 fetal deaths with an average fetal mortality of 32.5 per cent.

I did not mean to give the impression that we advised these patients to leave the hospital. Fourteen of them left the hospital although we would have preferred for them to stay. Fortunately they came back to the hospital with but little bleeding. I would not recommend that the patients with placenta previa leave the hospital unless they lived in close proximity and had easily available means of transportation.

(The remaining papers presented at the meeting will appear in the February issue of the JOURNAL).

Editorial

An International Congress on Obstetrics and Gynecology

In a previous editorial (November, 1947), we commented upon the desirability and importance of holding an international congress devoted to this important field of medicine. It is of interest to report that the Board of Directors of the American Committee on Maternal Welfare have agreed to sponsor such a conference in conjunction with the Fourth American Congress, and it was decided to hold it in New York City at the Hotel Pennsylvania, May 14 to 19, 1950. The place of meeting is the metropolis of the Western world, and is readily accessible by accepted modes of travel from all parts of the globe.

Preliminary plans include a program in which each morning of the four-day scientific sessions is to be devoted to formal presentation and discussion of a general topic. The afternoon sessions are to be given over to round table and informal discussions of these subjects. Tentatively selected are cancer of the female genitals, physiology and pathology of reproduction, and gynecologic procedures.

The field of obstetrics and gynecology involves wide implications, therefore it is important to include all interested groups—doctors, nurses, hospital administrators, public health personnel, and medical educators. An additional session at the close of the conference may be devoted to a presentation of economic and sociologic problems under the auspices of the National Federation of Obstetric-Gynecologic Societies.

In addition to the academic presentations to be made at the Congress there will be extensive technical and scientific exhibits, as well as social events. There will be opportunities for the participants from foreign countries to mingle with each other, peacefully to discuss their problems, and to become acquainted. There is nothing more likely to develop progress and interest in the advance of the speciality than such harmonious personal contacts. In conjunction with the Congress, it is likewise planned to develop clinics in various of the larger medical centers and hospitals of the country both before and afterwards, so that foreign visitors will have an opportunity to acquaint themselves with the advances of American institutions in this field.

Further details of the various activities will be announced as soon as plans are developed.

The executive offices of the Congress are located at 24 West Ohio Street, Chicago 10, Illinois, U. S. A., and all inquiries should be addressed to the General Chairman, Dr. Fred L. Adair.

The American profession is pleased to welcome the visitors to what is looked forward to as an unequalled opportunity for the advance of this important branch of medicine, for the commingling of people inspired by the same endeavors can only bespeak progress in a subject of global interest, for women-kind, healthy and well, means world-wide happiness.

Department of Reviews and Abstracts

Selected Abstracts

Mammary Glands

Cusmano, L.: Massive Pregnancy Hypertrophy of the Breast, *La Ginecologia* 12: 189, 1946.

True hypertrophy of the breast in which enlargement achieves enormous proportions, and is due particularly to increase of the glandular elements, is a rare event. It is mostly seen during puberty and is quite exceptional during pregnancy. Cusmano reviews the literature on the subject, to which papers of Dellepiane and Aimerich have mainly contributed, and describes a case of massive breast hypertrophy observed in a pregnant woman in the Department of Obstetrics of the Medical School of Parma.

The enormous hypertrophied mammae were quite symmetric, reached the groins of the patient in sitting position, and measured 60 cm. circumference at the base. The skin overlying the mammae appeared stretched, the nipples flattened, the areolae enlarged, reaching a diameter of 9 cm. Tortuosity of the superficial veins was present. The hypertrophic breast gave rise to a dull drag in sensation, and patient was obliged to support that breast during ambulation.

Milk secretion appeared two days after parturition. The flattened nipples made nursing impossible. Treatment was extremely conservative. Compressive bandage of the breast was used. Milk secretion stopped in a few days. The breast regressed to normal size in three months. Patient had previously shown in two former pregnancies moderate hypertrophy of the breast which, however, did not interfere with normal nursing.

GEMMA BARZILAI.

Malignancies

Cusmano, L.: Carcinoma of Cervix, Follow-Up Study of 281 Cases, *La Ginecologia* 8: 249, 1946.

L. Cusmano of the Gynecological Department of the Medical School in Parma reports statistical results in 281 cases of carcinoma of the cervix treated in the institute over a period covering ten years (1933 to 1944), and representing 3.6 per cent of the 7,666 gynecologic patients seen during this period. Age incidence in this group showed the presence of three cases under 30 years of age (1.06 per cent), of 39 cases between 30 and 40 years of age (13.78 per cent), 212 cases between 41 and 65 years of age (75.4 per cent), 27 over 60 years of age (9.6 per cent). Highest incidence in this group coincides with the average age incidence of carcinoma of the cervix. Carcinoma of the cervix in young women, however, appears to be exceedingly rare in the material observed in Parma. There were but 17 nulliparous women in the whole group, and the proportion of multiparous women is definitely higher than observed in average surveys. Multiparous women, however, distinctly predominate in Parma: women having more than five children reaching 49 per cent of the entire group observed in the Gynecological Department. No conclusion can therefore be drawn as to correlation between number of pregnancies and aptitude to develop cancer. It is noteworthy, however, that among the 281 cancer cases pluriparous women average a higher age in the development of cancer. Multiparous women with more

than nine children developed cancer at an average of 60 years, while nulliparas, uniparas and multiparas with less than five children showed cancer development at an average age of 50 years. In 11 per cent of the observed cases, other cases of cancer were present in the family, and in 4.3 per cent cervix carcinoma had been present in the mother. Nineteen and nine-tenths per cent of the cases observed in this group belonged to stage 1, 28.8 per cent to stage 2, 35 to stage 3, and 47 to stage 4. One hundred thirty-seven cases, i.e., 48 per cent of the whole group, were operable, 97, i.e., 34 per cent, were inoperable, and 47 were advanced cases. Eighty-five per cent of the cases in the group were treated by surgery, 125 by radium therapy, 59 by surgery and radiation therapy, 12 cases (incurable cases) received symptomatic therapy only. Five-year cures in cases treated through 1940 were observed in 55.3 per cent of cases treated by Wertheim method (throughout stage 1 or 2 cases), in 78 per cent of cases treated by total hysterectomy and followed by deep radiation therapy, and in 48 per cent of the cases treated by vaginal operation. Cases treated with radium therapy (including 65 per cent of stages 3 and 4) showed five-year cure in 33 per cent of the cases. Furthermore, of four cases of stump carcinoma, three were alive after five years. In this group, therefore, the best results were attained by total hysterectomy followed by deep x-ray therapy.

GEMMA BARZILAI.

Rocha, A. H.: Colposcopy in the Early Diagnosis of Cervical Cancer, *Obst. y Ginec. Latino-Am.* 4: 728-749, 1946.

In a series of 800 women whose cervixes were examined by means of the colposcope, the author found seven cases of early cancer. All of these patients came for gynecologic conditions other than for disturbances of the cervix. One woman was pregnant, one had prolapse of the uterus, three had syphilis and one had stenosing lymphogranulomatous proctitis. In all of the seven cases of cancer discovered by means of the colposcope, the diagnosis was verified by histologic examination. In addition to the seven cases of early carcinoma there were twenty-three cases of advanced cancer easily detectable without the colposcope. The author advocates amputation of the cervix in all cases where the cervix presents atypical epithelium. He further advises the use of the colposcope before every biopsy and every electrocoagulation of the cervix.

J. P. GREENHILL.

Campbell, James V., and Singman, David: Primary Ovarian Malignancy, *West. J. Surg.* 55: 263, 1947.

From the Highland Alameda County Hospital comes a report on 69 cases of primary ovarian malignancy. Most cases occurred in women past 60 years of age (24 per cent) and relatively few cases (12 per cent) under 40 years of age. The youngest was a dysgerminoma in a girl, aged 12 years. One case of arrhenoblastoma was seen in a girl, aged 14 years. The great majority fell into the class of papillary serous cystadenocarcinoma. There was an over-all five-year survival of 14 per cent (8 per cent for 46 malignant cystic tumors, 30 per cent for 10 solid tumors, and 100 per cent for three functional tumors). Several factors influence the prognosis: ascites, metastases, bilateral involvement, and the degree of cellular anaplasia. It was impossible to evaluate the value of x-ray therapy. Some patients apparently benefit from it. In others its use is followed by no consistent effects. Since the disease is one most commonly affecting the senile ovary, the question is posed, "Should all menopausal or postmenopausal enlargements or tumors of the ovary be removed, irrespective of size or symptoms?"

WILLIAM BICKERS.

Bianchi, P.: Carcinoma of Cervix and Corpus Uteri in Young Women, *Riv. d' Obstet. e Ginec.* 1: 113, 1946.

In young women under 35 years of age, P. Bianchi of the Gynecological Department of the University of Florence collected during the years 1922 to 1941 76 cases of carcinoma of the cervix uteri, and 11 cases of carcinoma of the body. In most of the cases, early symptoms had been neglected, and 49 of the 76 carcinomas of the cervix uteri were

considered inoperable, whereas all of the cases of carcinoma of the body could be operated upon. The cases of cervical carcinoma are graded by Bianchi according to the League of Nations' classification, and five-year end-results are as follows: in stages 1 and 2, in the group treated by surgery alone, a cure rate of 77 per cent was reached; in all groups that received surgical treatment plus irradiation a 100 per cent cure rate was attained. In the group treated by combined radium and x-ray irradiation the five-year cure rate was 85 per cent.

In cases belonging to stage 3, a 20 per cent cure rate was observed after surgical treatment followed by irradiation, and a 28 per cent rate in cases treated by combined radium and x-ray therapy. In group 4, no five-year cure was noted. Average five-year cure rate was 41.8 per cent. Cancer of the body was cured in 100 per cent of the cases. Primary surgical mortality was 9.3 per cent. This study confirms that patients of stage 3 are best treated by x-ray, patients of stages 1 and 2 by surgery. The Wertheim's panhysterectomy was used in most of the cases.

GEMMA BARZILAI.

Cesarean Section

Gray, T. Cecil: d-Tubocurarine in Cesarean Section, Brit. M. J. 4500: 444-445, 1947.

Gray, of the Whiston County Hospital, reports on his experience using d-tubocurarine as an inductant for cesarean section in 30 cases. Atropine, 0.65 mg., was given one hour preoperatively; followed by d-tubocurarine, 15.0 mg. injection; while some "kemithal" (cyclohexenyl-allyl-thiobarbiturate) 0.3 Gm. in 5.0 per cent solution, as an injection, followed the d-tubocurarine and anesthesia was subsequently maintained by cyclopropane.

All the infants, save two, cried lustily upon birth. The author observed an increased contractility of uterine muscle permitting him to omit usual postpartum "pituirin."

Because of the extremely light anesthesia the patients usually awakened, with rare postoperative retching or vomiting, as the dressings were applied. On occasion he did note slight residual signs of curarization at the end of an unusually quick operation, but only on two occasions was it necessary to utilize the antidotes "prostigium" and atropine. There was no urinary retention, ileus or eye symptoms in this series. Gray finds d-tubocurarine safe and valuable primarily in that its use prevented a long postoperative depression.

C. E. FOLSOME.

Peralta, Ramos A.: Abdominal Drainage in Unclean Cases of Cesarean Section, Obst. y ginec. Latino-Am. 4: 715-728, 1946.

The maternal mortality in unclean cases of cesarean section is still very high. Drainage such as is employed after the low, cervical operation is either useless or harmful, but drainage in cases of extraperitoneal cesarean section is effective and hemostatic. Our hope of reducing the death rate lies in the use of the antibiotics. However, the application of antibiotics in infected cases does not mean that we can discard the Porro operation, the extraperitoneal operation, nor drainage in selected cases. The author agrees with Sterling Mueller that the advice concerning appendicitis—namely: "In doubtful cases drain"—is as valid today as it was before the introduction of the sulfonamides.

J. P. GREENHILL.

Neme, B., and Esteves, J.: The Problem of Anesthesia in Cesarean Operations, An. brasil de ginec. 22: 174-185, 1946.

The authors analyzed the type of anesthesia used for 559 cesarean sections performed at the University of San Paulo. The incidence of the different types was as follows: spinal 74.9 per cent, inhalation 16.8 per cent, peridural 2.9 per cent, sacral 0.5 per cent, and intravenous 0.3 per cent. For subarachnoid block, hypertonic seurocaine solution was used in 95.7 per cent of the cases, and for the inhalation anesthetics ether and balsaform were

employed in 90.3 per cent of the cases. At the present time, cyclopropane gas-ether is preferred. The authors believe that hemorrhage is an important cause of death in cesarean section, and this complication is high after inhalation anesthesia. Peridural, local, and spinal anesthesia have a low incidence of hemorrhage.

A higher percentage of babies delivered under inhalation anesthesia required resuscitation than those delivered under spinal anesthesia. In order to reduce the death rate of 0.7 per cent and the incidence of hypotensive states of 2.3 per cent, spinal anesthesia should be administered only by trained anesthetists. Complementary anesthesia was necessary in 6.9 per cent of the spinal cases, 15.3 per cent of the peridural cases, 31.2 per cent of the local series, and 100 per cent of the intravenous group. The authors believe there are dangers of spinal anesthesia, but they no longer use this anesthetic in hypertension cases, and never with abruptio placentae.

J. P. GREENHILL.

Aguilo, A. J.: Peritoneal Sulfonamide Therapy During Cesarean Section at the San Borja Maternity, Bol. Soc. Chilean de Obstet. y Ginec. 11: 39-55, 1946.

According to the author, the prophylactic use of the sulfonamides during unclean cesarean sections is a great advance. In a series of 54 unclean cesarean sections in which the sulfonamides were used intraperitoneally, there were no deaths from peritonitis. The total death rate from peritonitis decreased to 1 per cent. Hence more women may be permitted a thorough test of labor than hithertofore, and cesarean section may be performed with safety. The addition of penicillin after operation improves still further, the good results obtained with the intraperitoneal use of the sulfonamides. However, the benefits derived from these drugs should not lead to errors in technique and carelessness. In the author's clinic the highest maternal mortality in the cesarean section cases is from shock and acute anemia, the result of total placenta previa (3 per cent).

J. P. GREENHILL.

Endocrinology

Price, Dorothy: The Influence of Maternal Hormones on the Reproductive Organs of Suckling Rats, Anat. Rec. 97: 519-545, 1947.

Price, of the University of Chicago, in the Hull Zoological Laboratory, in a well-documented article, exhibits evidence that ovarian androgens of lactating female albino rats reach the suckling young in effective amounts via the milk, and contribute in some degree to the growth of the male prostate and seminal vesicles.

The significance of the findings that maternal hormone stimulates growth in the reproductive tract of the suckling young rat lies in the fact that it proves that suckling animals have access to hormones from sources other than their own endocrine glands.

The author concludes further that there is no evidence from this study that estrogens from the mother have any effect upon the organs of suckling male or female albino rats.

C. E. FOLSOME.

Szarka, Von Alexander: The Pseudo-Pregnancy Picture Induced by Massive Doses of Follicular and Corpus Luteum Hormones, Gynaecologia 122: 338-346, 1946.

Szarka, of the Second Woman's Clinic of Budapest University, administered to an oöphorectomized woman 4,000,000 international units of follicular hormone and 400 mg. of crystalline progesterone. He was able to induce experimentally decidual-like changes similar to those seen in early pregnancy. He checked his observations both clinically and by endometrial study. He concludes his article with a discussion about several minor histologic points of difference in this specimen and those of early pregnancy, and attempts to correlate these details to the quantitative and chronological conditions of the two hormones.

C. E. FOLSOME.

Endometriosis

da Costa, C. C.: Extragenital Localization of Endometriosis, Obst. y Ginec. Latino-Am. 4: 387-409, 1946.

The author reports two cases of extragenital endometriosis situated in an umbilical scar. The first followed a cesarean section, and the other was associated with an adenomyoma of the round ligament. At the author's clinic during the last ten years, there were 33 cases of endometriosis among 2,285 operations (1.44 per cent). The distribution was as follows: tube 10, ovary 8, fibromyoma of the uterus 7, uterine corpus 3, round ligament 2, umbilical scar 2, and laparotomy scar 1. In the Brazilian literature he found reports of 24 cases of endometriosis of all types.

J. P. GREENHILL.

Fallon, John, Brosnan, James T., and Moran, William G.: Endometriosis, New England J. Med. 235: 669, 1946.

The authors discuss the etiology, symptoms, and treatment of endometriosis. They are of the opinion that endometriosis is an antivenereal disease—that is, it is associated with sexual unfulfillment. The prophylaxis seems to be early marriage and a child every few years.

Because endometriosis can be seen long before it can be felt, the practitioner should be as radical about advising early surgical exploration, and extirpation of all new growths of endometrial tissue, as the surgeon is conservative about castration.

JAMES P. MARR.

Macleod, Douglas: Endometriosis: A Surgical Problem, Brit. J. Surg. 34: 8, 1946.

The author deals mainly with extragenital endometriosis. The various theories of endometriosis are reviewed. Some of the more common manifestations of the disease are discussed. Various extragenital organs are reviewed, such as the perineum, umbilicus, bladder, ureter, laparotomy scar, bowel, small intestine, sigmoid, colon, and rectum. The author stresses the importance and difficulty of differentiating endometriosis of the rectum from malignancy. From a survey of all of the facts, it appears that endometriomas, wherever they occur, are the result of the endometrium taking upon itself lymphatic permeation. It is felt that endometriosis must be accorded a position somewhere between benign and malignant growths.

WILLIAM BERMAN.

Abell, Irvin, and Abell, Irvin, Jr.: Endometriosis, South. Surg. 13: 321, 1947.

There is no classical, clinical symptoms or physical findings which will consistently lead one to the correct diagnosis of endometriosis. It may mimic almost any other pelvic lesion, and occurs in association with other forms of pelvic pathology, even develops in company with carcinoma. Lesions of endometriosis have been found in all the pelvic organs, the inguinal region, abdominal wall, and at points distant from the pelvis, such as the lung. However, it shows a decided preference for the ovary, and in the series of cases here reported forced surgical castration in 60 per cent of the cases.

There are two theories of etiology, namely: (1) heteroplasia of tissue arising from coelomic epithelium; and (2) implantation theory of Sampson.

In support of the heteroplastic theory and in criticism of the implantation theory, the authors note that regurgitation of menstrual blood through the Fallopian tubes is never seen while operating upon women during menstruation and, furthermore, the endometrial tissue desquamated at menstruation is nonviable and, therefore, not capable of transplantation. Treatment cannot be generalized, but must be individualized on the basis of the patient's age, desire for children, and extent and location of the pathology.

WILLIAM BICKERS.

Correspondence

The Repeat Cesarean

To the Editor:

In the *American Journal of Obstetrics and Gynecology*, vol. 53, p. 914-926, June, 1947, an article written by Dr. C. T. O'Connor appeared regarding the risk involved in repeat cesarean section. Dr. O'Connor recommends the removal of the uterus in certain cases in order to lessen the risk to the mother. He quoted in part an article of mine in *Theological Studies*, December, 1944, vol. 5, p. 514 ff. The impression conveyed is that my remarks in *Theological Studies* are the basis for the moral aspects of his paper. This impression that I would approve of the conclusions as they appear in his paper is not warranted—and for two very important reasons: (1) I did not see Dr. O'Connor's paper as finished. (2) The case he now proposes appears to me to differ in at least one crucial point from the case I discussed in *Theological Studies*. The operation, if I read Dr. O'Connor's paper aright, is intended partially to prevent future dangerous conceptions. In fact, if I were not aware of his long record of service in Boston, and particularly in St. Elizabeth's Hospital, I would conclude from Dr. O'Connor's article that he was proposing hysterectomy in these cases as a more satisfactory method of sterilization than tubal resection.

In order to remove a source of confusion and error let me state my position.

Direct sterilization is forbidden; that is, sterilization chosen for its own sake, or chosen as a means of preventing dangerous conceptions. Operations which merely result in sterility are sometimes permitted on certain conditions; for example, first, that the resultant sterility is not chosen either as an end in itself or as a means to the patient's health, and secondly, that there exists a proportionately grave cause for permitting so grave a mutilation. Accordingly, I tentatively approved of hysterectomy in certain repeat cesareans on condition that the object of the operation was to safeguard the patient's health here and now, and not to safeguard it by preventing future dangerous conceptions, and on condition that sufficiently grave reasons existed for permitting the destruction of so important a function. This second condition was fulfilled if the clinical conclusions were correct, namely, that the radical procedure (cesarean hysterectomy) not only brought about a much smoother convalescence, but reduced by one-half the danger of death to the mother from the simple cesarean and its immediate consequences. And I gave this opinion in the further supposition that the case involved a repeat cesarean, and that the patient owed maternal duties to her living children. A reduction of mortality from 2 per cent to 1 per cent, or from 1.5 per cent to 0.5 per cent would be a very significant and important difference from a moralist's as well as from a surgeon's viewpoint, and would mean that the operation was at least twice as safe for the mother here and now. All these reasons seemed to me sufficient to permit, with the patient's consent, the resulting sterility.

My opinion was tentative, in that I wanted to hear what other moralists had to say before coming to a definite conclusion. So far, I have seen no arguments that would induce me to change my mind.

And my opinion was hypothetical and still is. For it is based on the hypothesis that Dr. O'Connor's clinical conclusions are established for practical purposes. Naturally, I am not the judge in these clinical matters.

I wish Dr. O'Connor would reassure me as to the purpose of the operation he recommends in his paper, for as it stands at present I cannot approve of it, and I do not feel that any Catholic moral theologian would.

JOHN C. FORD, S.J.
Professor of Moral Theology
Weston College

Sept. 15, 1947

Reply by Dr. O'Connor*To the Editor:*

It is true that Father Ford did not see my paper as finished. He was in Rome at that time, and, because of this and because I thought I understood his position and because I thought the further development was purely clinical, I did not contact Father Ford about the article as finished. I wish to state clearly now that I do not propose hysterectomy in any case as a more satisfactory method of sterilization than tubal resection. I am opposed to any form of sterilization which has as its purpose sterilization as such. As I go over my article again with Father Ford's statements before me, I believe that the impression could be obtained that one of my purposes in recommending cesarean hysterectomy was because it removed remote dangers, but my interest from the beginning was the relative immediate mortality of cesarean hysterectomy and the conservative operation. As I studied this subject more I became convinced of the immediate safety of the former. This conviction has been strengthened by the clinical results of Drs. Reis and deCosta whose paper appeared in the *J. A. M. A.*, vol. 134, June 28, 1947, and who believe that the mortality of cesarean hysterectomy is not any more than that of any supracervical hysterectomy and this, of course, is 0.5 per cent or less. I think that I may have created confusion in the minds of some Catholic doctors by mentioning on more than one occasion the remote aspects and the future welfare of the patient, but my prime and main interest and object was to stress the immediate safety of this operation in comparison with other procedures. Father Ford's statement of the moral aspects is acceptable to me and, indeed, welcomed because it will clarify both his position and mine. I understand that his position is tentative and hypothetical. The main purpose of the operation I recommended is that I believe the medical indications for cesarean hysterectomy in some cases should be extended, as I believe that the operation will be found to be much safer immediately, here and now, than the conservative operation. Every case, as Father Ford stressed, must be individualized, and the immediate safety of the patient is the controlling consideration. I have not in the past and do not now recommend any operation whose purpose is contraceptive.

CORNELIUS T. O'CONNOR, M.D.

BOSTON, MASS.

Sept. 17, 1947

Retroversion of the Uterus*To the Editor:*

I have just read Dr. Carl T. Javert's and Dr. H. B. Atlee's letters in the May JOURNAL discussing retroversion of the uterus as an etiological factor in abortion, nausea of pregnancy, backache, and sterility. Dr. Atlee decries the teaching of many, if not most textbooks, that retroversion is an important cause of these conditions. He, apparently, bases his opinion that it is not, on his clinical experience. Indeed, what other basis is there on which an opinion can be based? Dr. Javert upholds the opposite view. He buttresses his opinion by quoting as authorities two well-known writers. Neither Dr. Javert or these two writers seem to base their opinions on anything more substantial than the fact that they are "the accepted opinions of American authorities."

Several years ago, after twenty-four years of active practice, fourteen of them as a specialist in gynecology and obstetrics and visiting obstetrician on the staff of a large obstetric hospital and a large gynecologic service, I began to suspect that retroversion of the uterus was not a frequent cause of miscarriage. I consulted ten standard works. The weight of opinion was that retroversion is an important cause of miscarriage, but individual opinions varied from "retroversion is a not uncommon cause of abortion" to "the danger of abortion is not much greater than in the normal individual unless the uterus is adherent or becomes impacted in the pelvis." (As to impaction, a few words later.) Not one of the writers consulted gave any statistical data to support his opinions. It was my impression that most of these authorities, as did Dr. Javert, relied not on clinical data but on "authority;" that

the belief that retroversion of the pregnant uterus is a condition dangerous to either the fetus or the mother is a superstition passed on from one generation of medical men to another in the textbooks, without the verification of clinical observation.

About twenty years ago, for my own satisfaction and as a basis for an unpublished paper read before a small local medical club, 674 consecutive obstetric cases in the practice of my partner (the late Bertram H. Buxton) and myself were analyzed. Of these 674 cases, 325 were examined before the fourth month, by which time the retroverted pregnant uterus has either risen out of the pelvis or become incarcerated.

Among these 325 cases examined before the fourth month, the uterus was found to be in normal position in 271 (83 $\frac{1}{3}$ per cent), and in retroversion in 54 cases (16 $\frac{2}{3}$ per cent). Among the 271 cases with the uterus in normal position, there were 37 miscarriages or abortions (13.6 per cent).

Among the 54 cases with retroversion, there were six miscarriages or abortions (11.6 per cent).

The incidence of abortions and miscarriages was higher among the normal cases than among those with retroversion.

Thus my suspicion that, in our private practice at least, retroversion of the uterus was not a great threat to fetus or mother, was proved to be justified. None of these cases became incarcerated. Dr. Atlee has seen only one incarcerated uterus in approximately 4,000 cases. My experience coincides with that of Dr. Atlee. In forty years of an active obstetric practice, I can recall only three cases of incarceration of the pregnant uterus—none of them in my own patients, but seen in consultation with other men. I suspect that Dr. Atlee and I do not mean by "incarceration" the same condition as does Dr. Javert. The uterus truthfully cannot be said to be imprisoned in the pelvis until after the fourth month—the door of the pelvic prison is wide open up to the time the uterus has reached such a size that it cannot rise above the promontory of the sacrum or be replaced by manipulation from below. I suspect that if a three months' pregnant retroverted uterus was replaced with or without anesthesia because of backache and other pressure symptoms, Dr. Javert would consider it a case of incarceration; that probably Dr. Atlee would not. I certainly would not. I can account for the divergence in the experience of Dr. Atlee and that of Dr. Javert only on a basis of a confusion in terms or possibly that Dr. Atlee gives a retroverted uterus a chance to escape from its pelvic prison more often than does Dr. Javert.

From a series of cases so small as the one here reported no definitive conclusions can be drawn. Furthermore, it is impossible to know how many patients miscarry before consulting a doctor. However, this series would seem to indicate that when at the first examination a pregnant uterus is found to be retroverted, there is no cause to be alarmed. For many years I have made no effort to replace a retroverted pregnant uterus except to demonstrate to the patient how to assume the knee-chest position and, in symptomless cases, often not even that. The results have been just as satisfactory as when the uterus was replaced and a pessary inserted.

EDWARD S. BRACKETT, M.D.

PROVIDENCE 6, R. I.
August 29, 1947

Necrology

JAMES R. GOODALL, M.D., of Montreal, professor of obstetrics and gynecology at McGill University since 1912, recipient of many honorary degrees, participant in World War I as a medical officer, a frequent contributor to American and English journals, well known for his work on endometriosis, died suddenly on Sept. 25, 1947, at the age of 77 years.

ROBERT MEYER, M.D., notable embryologist and gynecologic pathologist, a field in which he pioneered in all of its branches, migrating to this country from his native Germany during the Hitler regime and settling in Minneapolis as a member of the staff of the University, died there on Dec. 13, 1947, at the age of 84 years. A prodigious scientific output included his monumental work on the embryology of the vagina and various fetal anomalies, his studies on ovarian tumors, on the life cycle of the corpus luteum, the correlation of the ovarian and endometrial cycles, many contributions to the knowledge of genital cancer, as well as hydatidiform mole and chorionepithelioma.

CURTIS F. BURNHAM, M.D., of Baltimore, long associated with the Kelly Clinic, and prominent in the development of radiotherapeutic procedures in gynecology, associate professor at Johns Hopkins, born in Richmond, Kentucky, Jan. 17, 1877, died in Baltimore, Dec. 17, 1947, at the age of 70 years.

Item

American Board of Obstetrics and Gynecology, Inc.

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Friday, Feb. 6, 1948.

Arrangements will be made so far as is possible for candidates to take the Part I examination (written paper and submission of case records) at places convenient for them. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held May 16-22, 1948, in Washington, D. C. Notice of the exact time and place of the Part I and Part II examinations will be sent all candidates well in advance of the examination date.

For further information and application blanks address Paul Titus, M.D., Secretary, 1015 Highland Building, Pittsburgh, Pa.

PAUL TITUS, M.D.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

- American Gynecological Society.** (1876) *President*, Emil Novak, Baltimore, Md. *Secretary*, Norman Miller, Ann Arbor, Mich. Annual meeting to be held at Williamsburg, Va., May 24, 25, and 26, 1948.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** (1888) *President*, A. D. Campbell, Montreal, Quebec. *Secretary*, James R. Bloss, 418 11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 4-6, 1947.
- Central Association of Obstetricians and Gynecologists.** (1929) *President*, Earl C. Sage, Omaha, Neb. *Secretary-Treasurer*, John I. Brewer, 104 South Michigan Ave., Chicago, Ill. Annual meeting Louisville, Ky., Oct. 23, 24, and 25, 1947.
- South Atlantic Association of Obstetricians and Gynecologists.** (1938) *President*, J. Randolph Perdue, Miami, Fla. *Secretary*, E. D. Colvin, 1259 Clifton Road, N.E., Atlanta, Ga. Annual meeting at Augusta, Ga., February 12 to 14, 1948.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, William F. Mengert, Dallas, Texas. *Secretary*, A. B. Hunt, Mayo Clinic, Rochester, Minn. Annual meeting June, 1947.
- New York Obstetrical Society.** (1863) *President*, Albert H. Aldridge. *Secretary*, R. G. Douglas, 530 East 70th St., New York City. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** (1868) *President*, John B. Montgomery. *Secretary*, James P. Lewis, 1930 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** (1878) *President*, Aaron E. Kanter. *Secretary*, Edward M. Dorr, 30 N. Michigan Ave., Chicago 2, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** (1890) *President*, Alexander E. Dunbar. *Secretary*, William T. Daily, 142 Joralemon St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society.** (1929) *President*, Lawrence Wharton. *Secretary-Treasurer*, John W. Haws, 9 E. Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.
- Cincinnati Obstetrical Society.** (1876) *President*, Carroll J. Fairo. *Secretary*, Joseph G. Crotty, 136 West McMillan St., Cincinnati, Ohio. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, W. O. Johnson. *Secretary*, W. E. Oldham, 842 Barrett Avenue, Louisville, Ky. Meetings fourth Monday of each month from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology.** *President*, Ronald Frazier. *Secretary-Treasurer*, Gifford D. Seitz, 919 Taylor St. Bldg., Portland 5, Ore. Meetings last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** (1934) *President*, Joseph A. Hepp. *Secretary*, Clarence H. Ingram, Jr., 6004 Penn Avenue, Pittsburgh 6, Pa. First Monday of October, December, February, April, and June.
- Obstetrical Society of Boston.** (1861) *President*, Frederick J. Lynch. *Secretary*, Paul A. Younge, 1101 Beacon Street, Brookline, Mass. Third Tuesday, October to April, Harvard Club.
- New England Obstetrical and Gynecological Society.** (1929) *President*, Arthur E. G. Edgelow, Springfield, Mass. *Recorder*, Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society.** (1931) *President*, Henry N. Shaw. *Secretary-Treasurer*, William Benbow Thompson, 6253 Hollywood Blvd., Los Angeles, Calif. Next meeting in Seattle, Wash., Oct. 1 to 4, 1947.
- Washington Gynecological Society.** (1933) *President*, Lawrence Lee Cockerille. *Secretary*, Raymond T. Holden, 3111 16 Street, N.W., Washington 10, D. C. Fourth Saturday, October, November, January, March, May.
- New Orleans Obstetrical and Gynecological Society.** (1924) *President*, Dr. Earl Conway Smith. *Secretary*, John S. Herring, Audubon Bldg., New Orleans 16, La. Meetings held October, November, January, March, and May.
- St. Louis Gynecological Society.** (1924) *President*, Joseph A. Hardy, Jr. *Secretary*, Paul F. Fletcher, 634 North Grand Ave., St. Louis 3, Mo. Meetings second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** (1929) *President*, Albert M. Vollmer. *Secretary*, Daniel G. Morton, University of California Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.

*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.

- Texas Association of Obstetricians and Gynecologists.** (1930) *President*, T. F. Bunkley. *Secretary*, J. McIver, 714 Medical Arts Bldg., Dallas, Tex.
- Michigan Society of Obstetricians and Gynecologists.** (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President*, Clarence E. Toshach. *Secretary*, John P. Ottaway, 1551 Woodward Ave., Detroit, Mich. Meetings first Tuesday of each month from October to May (inclusive).
- Central New York Association of Obstetricians and Gynecologists.** (1938) *President*, Raymond J. Pieri. *Secretary*, Nathan N. Cohen, 713 E. Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.
- Alabama Association of Obstetricians and Gynecologists.** *President*, Gilbert F. Douglas. *Secretary*, Hunter Brown, 1922 South Tenth Ave., Birmingham, Ala.
- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society.** (1941) *President*, Carl M. Helwig. *Secretary*, Roger E. Stewart, Stimson Bldg., Seattle, Wash. Meetings held on third Wednesday of each month.
- Denver Obstetrical and Gynecological Society.** (1942) *Secretary*, Emmett A. Mechler, 1612 Tremont St., Denver, Colo.
- Wisconsin Society of Obstetrics and Gynecology.** (1940) *President*, J. M. Freeman. *Secretary-Treasurer*, Lionel T. Servis, 425 East Wisconsin Ave., Milwaukee. Meetings held in May and October.
- San Diego Gynecological Society.** (1937) *President*, R. C. Hall. *Secretary*, D. Dalton Deeds, 2001 Fourth Ave., San Diego, Calif. Meetings held on the last Wednesday of each month.
- North Dakota Society of Obstetrics and Gynecology.** (1938) *President*, Ralph E. Leigh, Grand Forks. *Secretary*, G. Wilson Hunter, 807 Broadway, Fargo, N. D.
- Virginia Obstetrical and Gynecological Society.** (1936) *President*, S. E. Oglesby. *Secretary*, L. L. Shamburger, 628 State Office Bldg., Richmond 19, Va. Next meeting not announced.
- Columbus Obstetric and Gynecologic Society.** (1944) *President*, Dana Cox. *Secretary*, Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held fourth Wednesday of each month.
- Naussau Obstetrical Society.** (1944) *President*, Austin B. Johnson. *Secretary*, Robert S. Millen, Westbury, N. Y. Meetings, bimonthly from October to May.
- Bronx Gynecological and Obstetrical Society.** (1924) *President*, George Muscillo. *Secretary*, Milton D. Klein, 1882 Grand Concourse, New York 57, N. Y. Meetings, fourth Monday monthly from October to May.
- Washington State Obstetrical Society.** (1936) *President*, John H. Fiorino, Everett. *Secretary*, H. H. Skinner, Yakima. Meetings, first Saturday of April and October.
- Kansas City Obstetrical and Gynecological Society.** (1922) *President*, Thomas J. Sims. *Secretary*, LeRoy Goodman, 702 Bryant Bldg., Kansas City, Mo. Meetings, last Thursday, September, November, January, and March; first Thursday, May, University Club.
- Los Angeles Obstetrical and Gynecological Society.** (1914) *President*, Carl E. Krugmeier. *Secretary-Treasurer*, A. M. McCausland, 3780 Wilshire Blvd., Los Angeles, Calif.
- North Carolina Obstetrical and Gynecological Society.** (1932) *President*, Wallace B. Bradford. *Secretary*, Richard B. Dunn. Meetings semiannually.
- The Society of Obstetricians and Gynecologists of Canada.** (1944) *President*, William A. Scott. *Secretary*, James Goodwin, 516 Medical Arts Bldg., Toronto, 5. Meetings held annually, date of next meeting to be announced later.
- Akron Obstetrical and Gynecological Society.** (1946) *President*, L. L. Bottsford. *Secretary-Treasurer*, N. E. Wentsler, 1029 Second National Bldg., Akron 8, Ohio.
- Minnesota Society of Obstetrics and Gynecology.** *President*, L. M. Randall. *Secretary*, Russell J. Moe, 205 West Second St., Duluth, Minn. Meetings held spring and fall.
- Miami Obstetrical and Gynecological Society.** (1946) *President*, M. C. Wilson. *Secretary*, George A. Mitchell, Huntington Bldg. Meetings, second Thursday in January, March, May, and November.
- Omaha Obstetrical and Gynecological Society.** (1947) *President*, M. E. Grier. *Secretary*, B. V. Reaney, 1116 Medical Arts Bldg., Omaha 2, Neb. Meetings held third Wednesday in January, March, May, September, November.
- Oklahoma City Obstetrical and Gynecological Society.** (1940) *President*, Le Roy H. Sadler. *Secretary-Treasurer*, John W. Records, 301 Northwest 12 Street, Oklahoma City.
- Cleveland Obstetrical and Gynecological Society.** (1947) *President*, Robert E. Faulkner. *Secretary*, G. Keith Folger, 10515 Carnegie Ave. Meetings on fourth Tuesday of September, November, January, March, and May at University Club, 3813 Euclid Ave., Cleveland 15, Ohio.
- New Jersey Obstetrical and Gynecological Society.** (1947) *President*, Samuel A. Cosgrove. *Secretary*, Benjamin Daversa, Spring Lake, N. J. Meetings semiannually.
- Honolulu Obstetrical and Gynecological Society.** (1947) *President*, Colin C. McCorriston. *Secretary-Treasurer*, K. S. Tom, 296-E South Vineyard Street, Honolulu 39, Hawaii. Meetings third Monday of each month, Mabel Smyth Building.